Conceptmodules richtlijn Antitrombotisch beleid

INITIATIEF
Nederlandse Internisten Vereniging

IN SAMENWERKING MET
Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie
Nederlandse Orthopaedische Vereniging
Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose
Nederlandse Vereniging van Ziekenhuisapothekers
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Nederlandse Vereniging voor Neurologie
Nederlandse Vereniging voor Obstetrie en Gynaecologie
Nederlandse Vereniging voor Radiologie
Nederlandse Vereniging voor Thoraxchirurgie
Stichting Harteraad

MET ONDERSTEUNING VAN
Kennisinstituut van de Federatie Medisch Specialisten

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De richtlijnontwikkeling werd gefinancierd uit de Kwaliteitsgelden Medisch Specialisten (SKMS).

Colofon

CONCEPTMODULES RICHTLIJN ANTITROMBOTISCH BELEID

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Startpagina

Waar gaat deze richtlijn over?

Meer dan 1 miljoen mensen in Nederland gebruiken enige vorm van antistolling of plaatjesaggregatieremming ter preventie en/of behandeling van een trombotische aandoening. Operaties en andere ingrepen bij deze patiënten komen veel voor. Vele specialismen zijn hierbij betrokken. Omdat vrijwel elke klinische werkende zorgverlener – arts, tandarts of verpleegkundige – te maken krijgt met antitrombotische therapie is het van verstrekkend belang dat er een richtlijn Antitrombotische therapie is. Een multidisciplinaire richtlijn is onontbeerlijk voor de patiënt die met deze therapie soms meer specialismen bezoekt.

Op het Nederlands Kennisplatform Antistolling https://www.allesoverantistolling.nl/ vindt u meer informatie over antistolling, zoals regionale samenwerkingsverbanden en e-learning. Ook kunt u vragen stellen aan antistolling-experts.

Voor wie is deze richtlijn bedoeld?

Deze richtlijn richt zich op wat volgens de huidige maatstaven de beste zorg is voor patiënten met antitrombotische therapie. Deze richtlijn is bestemd voor alle zorgverleners in de tweede en derde lijn die betrokken zijn bij de zorg voor patiënten met een antitrombotische behandeling dan wel tromboseprofylaxe .

Voor patiënten

Antitrombotisch beleid gaat over het behandelen of voorkomen van trombose. Bij trombose vormt zich een bloedstolsel in een bloedvat. Hierdoor wordt de bloedtoevoer naar of van de weefsels verminderd. Weefsel kan daardoor bij afgesloten toevoer afsterven. Trombose kan tot (ernstige) klachten leiden, zoals heftige pijn, zwelling van het been, hartkloppingen, benauwdheid, kortademigheid of flauwvallen. Ook kan het zijn dat je een arm, been of een ander deel van je lichaam niet meer (goed) kunt bewegen of bijvoorbeeld niet meer goed kunt praten of slikken (uitvalsverschijnselen). Mensen kunnen er ook door overlijden. In Nederland gebruiken meer dan één miljoen mensen een medicijn ter preventie en/of behandeling van trombose.

Als trombose voorkomt in een slagader, heet dat arteriële trombose. Komt trombose voor in een ader, dan spreekt men van veneuze trombose. Onder arteriële trombose vallen bijvoorbeeld een hersen- en hartinfarct. Bij veneuze trombose gaat het om longembolie of diep veneuze trombose (DVT), ook wel trombosebeen genoemd. Deze twee aandoeningen heten samen ook wel veneuze trombo-embolie (VTE).

Meer informatie over trombose is te vinden op Thuisarts:

- https://thuisarts.nl/trombosebeen
- https://thuisarts.nl/beroerte
- https://thuisarts.nl/longembolie
- Ik gebruik een bloedverdunner (DOAC). Waar moet ik op letten?
- Ik gebruik een bloedverdunner (cumarine). Waar moet ik op letten?
- Ik gebruik een bloedverdunner (bloedplaatjesremmer). Waar moet ik op letten?
- Ik ben vergeten mijn bloedverdunner te slikken

Patiënteninformatie vindt u op het Nederlands Kennisplatform Antistolling:

- https://www.allesoverantistolling.nl/patient/

Informatie over geneesmiddelen kunt u vinden op apotheek.nl

- acenocoumarol | Apotheek.nl
- fenprocoumon | Apotheek.nl
- edoxaban | Apotheek.nl
- apixaban | Apotheek.nl
- rivaroxaban | Apotheek.nl
- dabigatran | Apotheek.nl
- Longembolie | Apotheek.nl
- Hartritmestoornissen | Apotheek.nl
- Trombose | Apotheek.nl
- Trombosebeen | Apotheek.nl

Hoe is de richtlijn tot stand gekomen?

Het initiatief voor deze richtlijn is afkomstig van de Nederlandse Internisten Vereniging (NIV). De richtlijn is opgesteld door een multidisciplinaire commissie. In de kerngroep zaten vertegenwoordigers vanuit de internisten, orthopeden, chirurgen, kinderartsen, cardiologen, neurologen, huisartsen en mdl-artsen. In de klankbordgroep waren de volgende disciplines vertegenwoordigd: internisten, mdl-artsen, kinderartsen, longartsen, klinisch chemici, intensivisten, klinisch geriaters, gynaecologen, radiologen, (ziekenhuis)apothekers, dermatologen, cardio-thoracaal chirurgen, mka-chirurgen, en de Harteraad.

Toepassen

- De landelijke transmurale afspraak (LTA) antistollingszorg geeft richting aan de samenwerking tussen de medisch specialist, huisarts, trombosedienst, openbaar apotheker, specialist ouderengeneeskunde, tandartsen en mondhygiënisten.
- Het doel van het Nederlands Kennisplatform Antistolling is om kennis, instrumenten en initiatieven op het gebied van antistollingszorg samen te brengen en uitwisseling van kennis te bevorderen.

Status van de richtlijn

De richtlijn Antitrombotisch beleid maakt deel uit van het cluster Antitrombotisch beleid. De richtlijnmodules zullen jaarlijks beoordeeld worden op geldigheid en relevantie.
Ook kunnen nieuwe modules aan de richtlijn worden toegevoegd wanneer er relevante nieuwe ontwikkelingen hebben plaatsgevonden of wanneer dit anderzijds belangrijk wordt geacht.

Verantwoording

Autorisatie en geldigheid

Zie specificaties per richtlijnmodule.

Algemene gegevens

De ontwikkeling/herziening van deze richtlijnmodule werd ondersteund door het Kennisinstituut van de Federatie Medisch Specialisten (www.demedischspecialist.nl/kennisinstituut) en werd gefinancierd uit de Kwaliteitsgelden Medisch Specialisten (SKMS). Patiëntenparticipatie bij deze richtlijn werd medegefinancierd uit de Kwaliteitsgelden Patiënten Consumenten (SKPC) binnen het programma KIDZ.
De financier heeft geen enkele invloed gehad op de inhoud van de richtlijnmodule.

Samenstelling werkgroep

Voor het ontwikkelen van de richtlijnmodule is in 2021 een multidisciplinaire werkgroep ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen (zie hiervoor de Samenstelling van de werkgroep) die betrokken zijn bij de zorg voor patiënten die antitrombotische therapie dan wel tromboseprofylaxe gebruiken.

Belangenverklaringen

De Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling is gevolgd. Alle werkgroepleden hebben schriftelijk verklaard of zij in de laatste drie jaar directe financiële belangen (betrekking bij een commercieel bedrijf, persoonlijke financiële belangen, onderzoeksfinanciering) of indirecte belangen (persoonlijke relaties, reputatiemanagement) hebben gehad. Gedurende de ontwikkeling of herziening van een module worden wijzigingen in belangen aan de voorzitter doorgegeven. De belangenverklaring wordt opnieuw bevestigd tijdens de commentaarfase.
Een overzicht van de belangen van werkgroepleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten.

Werkgroeplid	Functie	Nevenfuncties	Gemelde belangen	Ondernomen actie
Huisman (voorzitter)	Internist vasculaire geneeskunde	• voorzitter Dutch Thrombosis Network – onbetaald • voorzitter Nationaal Kennisplatform Antistollingszorg – onbetaald • medisch leider Trombosedienst Leiden - detachering LUMC	• ZonMW Dutch Healthcare Fund – herseninfarct na covid-19 en register van patienten met atrium fibrilleren • NHS – herseninfarct na covid-19 • Boehringer Ingelheim – register atriumfibrilleren – afgesloten • Bristol-Myers Squibb/Pfizer – VTE behandeling bij patienten met maligniteit – afgesloten • Bayer Health Care - VTE behandeling bij patienten met	Geen restricties

			maligniteit – afgesloten • Aspen – webinar anti-Xa bepaling bij LMWH – afgesloten • Daiichi-Sankyo – deelname studie cancer associated thrombosis – afgesloten → op geen van deze projecten projectleider, betreft unrestricted grants en veelal financiering promotietrajecten.	
Banne Nemeth	Orthopedisch chirurg in opleiding	Postdoc klinische epidemiologie en orthopedie, LUMC	Trombosestichting - "VTE following total hip and knee arthroplasty: prediction is the future"	Geen restricties
Harmen Ettema	Orthopedisch chirurg Isala zwolle	Geen	ZonMW, Distinct trial, tromboseprofylaxe bij orthopedische ingrepen, geen projectleider	Geen restricties
Jonathan Coutinho	neuroloog Amsterdam UMC	Geen	• ZonMw, Hartstichting, Eurostars, Trombosestichting, Europese Unie, Health-Holland, NWO, onderzoek naar diagnostiek en behandeling van een beroerte • Bayer - Pacific stroke en Oceanic stroke study, onderzoek naar inzet van nieuw middel bij patienten met een beroerte, national leader en SC member) • Co-founder TrianecT BV • Boehringer Ingelheim - RESPECT CVT, vergelijking dabigatran Etexilate met Warfarin, SC member, • AstraZeneca, Portola - ANNEXA-I studie, onderzoek naar inzet van Andexanet alfa bij patienten met intracraniele bloeding, national leader • fellow European Stroke Organization • lid richtlijn commissie ESO over cerebrale sinustrombose • editorial board member Stroke en Journal of Neurology	Restricties t.a.v. besluitvorming modules over andexanet alfa bij bloedingen geen restricties ten gevolge van rol pacific stroke study en dabigatran etixilate/warfarin bij CVT, aangezien deze patientengroep en geen onderwerp zijn van deze richtlijnherziening.

			• leadership International cerebral venous thrombosis consortium	
Klok	Internist vasculaire geneeskunde LUMC Leiden	• Bestuur NVIVG • Bestuur ESC werkgroep pulmonale circulatie • Bestuur ISTH SSC werkgroep diagnostische en predictieve variabelen (tot 2024) • Bestuur Dutch Thrombosis Network • Gastwetenschapper Universiteit Mainz (Duitsland) • Medisch leider Trombosedienst Leiden (tot 1-1-25)	• Bayer, Leo Pharma en BSCI – voorzitter van een internationale werkgroep om een standaard set van uitkomsten (ICHOM) te maken voor VTE – inmiddels afgesloten • Actelion en The Netherlands Organisation for Health Research and Development - mede-aanvrager van 3 ZonMw beurzen voor onderzoek naar voorkomen van VTE en herseninfarcten bij COVID-19 patiënten (DC&TC en CORONIS consortium - DC&TC wordt ook ondersteund door TSN en een unrestricted grant van Actelion voor diagnostiek deel - afgesloten • The Dutch Thrombosis Association -onderzoek naar nieuwe beeldvormende technieken van trombose • The Dutch Heart Foundation - lange termijn prognose van longembolie - afgesloten • the Horizon Europe Program - voorzitter van een Europees consortium dat tot doel heeft het gebruik van antitrombotische medicatie in de laatste levensfase te optimaliseren	Geen restricties
Kruip	Hematoloog en directeur Kwaliteit & Patientenzorg, Erasmus MC, betaald	• Medisch leider trombosedienst Star-shl (0.2FTE), gedetacheerd vanuit Erasmus MC, betaald • voorzitter Federatie Nederlandse Trombosedienst en (FNT), onbetaald	• Horizon Europe programme • Trombosestichting/ZonMw • Sprekers vergoedingen gehad van Sobi, Roche en Bristol Myers Squibb; betaling aan het Erasmus MC	Geen restricties

		• RvC Lenticure, onbetaald • RvT Trombosestichting, onbetaald		
Maarten Tushuizen	MDL-arts LUMC	Geen	Maag-Lever-Darmstichting (MLDS)	Geen restricties
Marc Brouwer	Cardioloog Radboudumc	Geen	Nee	Geen restricties
Paul Smits	huisarts, zelfstandig	Coördinator onderwijscommissie harvaatHAG	geen	Geen restricties
Monique Suijker	Kinderarts-hematoloog werkzaam bij Van Creveldkliniek, UMCU	Geen	Geen lopende studies Bayer en Janssen - Einstein Jr studie - gebruik Rivaroxaban bij kinderen – afgesloten	Geen restricties
Arno Wiersema (teruggetrokken, tot 2024)	Vaatchirurg, Dijklander ziekenhuis	Geen	ZonMw, Amsterdam UMC, Dijklander zh en Medtronic - www.action-1.nl - betreft onderzoek naar rol van heparine bij een open buikslagader operatie, rol als projectleider	Restricties ten aanzien van besluitvorming over heparine.
Michiel Warlé (vanaf 2024)	Vaatchirurg Radboudumc	Werkgroep Landelijk Kennisplatform Antistolling	ZEGG/ZonMw- GENPAD studie (Cyp2c19 genotypering bij Clopidogrel en perifeer arterieel vaatlijden - hoofdonderzoeker	Geen restricties
Nick van Es (vanaf 2023)	Internist-vasculaire geneeskunde, Amsterdam UMC, locatie AMC	Geen	• Eenmalige adviesraad Pfizer (2019) • Deelname Podcast LEO Pharma (2024) • Sprekersvergoeding Werfen en Amgen (2024) • Trombosestichting – PREVENT (PREdicting VENous Thromboembolism in pancreatic cancer patients) • NWO - Blood vessels-on-chip to understand and target COVID-19 intravascular coagulation • Anthos Therapeutics, ASTER-study en MAGNOLIA-study, effectiviteit en veiligheid van abelacimab (niet geregistreerd middel) in patienten met kankergerelateerde trombose, rol als national lead investigator.	Geen restricties

Leentjens (vanaf 2023)	Internist-vasculair geneeskundige, Radboudumc	Geen	• Astra Zeneca - scientific steering comité van database studie over bloedingen bij ptn die Xa remmers gebruiken (apixaban, edoxaban • Adviesraad Viatris (tot begin 2024) • Synapse B.V. – studie naar interactie tussen hemostase en inflammatie bij patiënten met een herseninfarct op jonge leeftijd	Geen restricties
Actieve klankbordgroepleden				
Esther Nossent	Longarts Amsterdam UMC	Geen	• Janssen, Bayer, MSD, United Therapeutics, Ferrer - OPTICS • Boehringer Ingelheim B.V., AbbVie, Breathomix – P402 ILD-extension • Owlstone en PEXAS	Geen restricties
Heleen van Ommen	Hoofd afd. Kinderhematologie & kinderoncologie Erasmus MC Sophia Kinderziekenhuis	Geen	• Daiicho Sankyo - Fase 3 trial effectiviteit van edoxaban voor behandeling van trombose bij kinderen, local PI en steeringCie - afgesloten • Octopharma - Microscopic evaluation of clots in ECMO systems, rol als PI • BI/BMS en INVENT – chair IPTN ThromPED registry (international observational registry/study of children with thrombosis, • Adviseur voor verschillende farmaceuten voor ontwikkeling van onderzoek van antistollingsmiddelen of antidota bij kinderen zoals Asundexian (Bayer BV), andexanet (Astra Zeneca) – afgesloten	Geen restricties
Eric Tjwa	MDL arts, Radboudumc	Geen	Geen	Geen restricties
Hans-Martin Otten (vanaf 2024)	Internist Meander MC	Lid METC UMCU, betaald	• Eenmalig advies aan Leo Pharma: standpunten over de zorg bij patiënten met VTE en kanker in NL (19-11-2019)	Geen restricties

			• ANT-007 & ANT-008 multi-center studies, abelcimab vs apixaban bij kankergerelateerde VTE, participatie in Meander MC • Hukusai-study, participatie - afgesloten • Einstein-study, adjudicatie-cie - afgesloten	
Noa Rosenberg (vanaf 2024)	Beleidsadviseur		Geen	Geen restricties

Inbreng patiëntenperspectief

Er werd aandacht besteed aan het patiëntenperspectief door uitnodigen van Stichting Harteraad voor de schriftelijke knelpuntenanalyse en door een patientvertegenwoordiger van Stichting Harteraad toe te voegen aan de klankbordgroep. De verkregen input is meegenomen bij het opstellen van de uitgangsvragen, de keuze voor de uitkomstmaten en bij het opstellen van de overwegingen (zie alinea waarden en voorkeuren van patiënten).De conceptrichtlijn is tevens voor commentaar voorgelegd aan Stichting Harteraad en de eventueel aangeleverde commentaren zijn bekeken en verwerkt.

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijnmodule is conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uitgevoerd om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema op de Richtlijnendatabase).

Module	**Uitkomst raming**	**Toelichting**
Module Diagnostiek VTE	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

Module	**Uitkomst raming**	**Toelichting**
Module follow-up VTE	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

Module	**Uitkomst raming**	**Toelichting**
Module tromboseprofylaxe volwassenen met maligniteit	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

Module	**Uitkomst raming**	**Toelichting**
Module tromboseprofylaxe kinderen met maligniteit	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

Module	Uitkomst raming	Toelichting
Module behandeling intermediair-hoog risico longembolie	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

Module	Uitkomst raming	Toelichting
Module behandeling buikvene trombose	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

Module	Uitkomst raming	Toelichting
Module antitrombotisch beleid na bariatrische chirurgie	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

Module	Uitkomst raming	Toelichting
Module antitrombotisch beleid rondom endoscopische ingrepen	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

Module	Uitkomst raming	Toelichting
Module herstarten antistollingstherapie na bloeding	[geen/ mogelijk] financiële gevolgen	[plaatsen desbetreffende uitkomst 1, 2, 3, 4 of 5]

De kwalitatieve raming volgt na de commentaarfase.

Werkwijze

AGREE

Deze richtlijnmodule is opgesteld conform de eisen vermeld in het rapport Medisch Specialistische Richtlijnen 2.0 van de adviescommissie Richtlijnen van de Raad Kwaliteit. Dit rapport is gebaseerd op het AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II; Brouwers, 2010).

Knelpuntenanalyse en uitgangsvragen

Tijdens de voorbereidende fase inventariseerde de werkgroep de knelpunten in de zorg voor patiënten die antitrombotische therapie dan wel profylaxe gebruiken. De leden van de werkgroep en klankbordgroep beoordeelden de aanbevelingen uit alle richtlijnmodules op noodzaak tot revisie. Tevens zijn er knelpunten aangedragen tijdens de schriftelijke knelpuntenanalyse. Een verslag – inclusief de lijst van partijen die benaderd zijn - hiervan is opgenomen onder aanverwante producten.

Op basis van de uitkomsten van de knelpuntenanalyse zijn door de werkgroep concept-uitgangsvragen opgesteld en definitief vastgesteld.

Uitkomstmaten

Na het opstellen van de zoekvraag behorende bij de uitgangsvraag inventariseerde de werkgroep welke uitkomstmaten voor de patiënt relevant zijn, waarbij zowel naar gewenste

als ongewenste effecten werd gekeken. Hierbij werd een maximum van acht uitkomstmaten gehanteerd. De werkgroep waardeerde deze uitkomstmaten volgens hun relatieve belang bij de besluitvorming rondom aanbevelingen, als cruciaal (kritiek voor de besluitvorming), belangrijk (maar niet cruciaal) en onbelangrijk. Tevens definieerde de werkgroep tenminste voor de cruciale uitkomstmaten welke verschillen zij klinisch (patiënt) relevant vonden.

Methode literatuursamenvatting

Een uitgebreide beschrijving van de strategie voor zoeken en selecteren van literatuur is te vinden onder 'Zoeken en selecteren' onder Onderbouwing. Indien mogelijk werd de data uit verschillende studies gepoold in een random-effects model. Review Manager 5.4 werd gebruikt voor de statistische analyses. De beoordeling van de kracht van het wetenschappelijke bewijs wordt hieronder toegelicht.

Beoordelen van de kracht van het wetenschappelijke bewijs

De kracht van het wetenschappelijke bewijs werd bepaald volgens de GRADE-methode. GRADE staat voor 'Grading Recommendations Assessment, Development and Evaluation' (zie http://www.gradeworkinggroup.org/). De basisprincipes van de GRADE-methodiek zijn: het benoemen en prioriteren van de klinisch (patiënt) relevante uitkomstmaten, een systematische review per uitkomstmaat, en een beoordeling van de bewijskracht per uitkomstmaat op basis van de acht GRADE-domeinen (domeinen voor downgraden: risk of bias, inconsistentie, indirectheid, imprecisie, en publicatiebias; domeinen voor upgraden: dosis-effect relatie, groot effect, en residuele plausibele confounding).
GRADE onderscheidt vier gradaties voor de kwaliteit van het wetenschappelijk bewijs: hoog, redelijk, laag en zeer laag. Deze gradaties verwijzen naar de mate van zekerheid die er bestaat over de literatuurconclusie, in het bijzonder de mate van zekerheid dat de literatuurconclusie de aanbeveling adequaat ondersteunt (Schünemann, 2013; Hultcrantz, 2017).

GRADE	Definitie
Hoog	• er is hoge zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • het is zeer onwaarschijnlijk dat de literatuurconclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Redelijk	• er is redelijke zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • het is mogelijk dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Laag	• er is lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • er is een reële kans dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Zeer laag	• er is zeer lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • de literatuurconclusie is zeer onzeker.

Bij het beoordelen (graderen) van de kracht van het wetenschappelijk bewijs in richtlijnen volgens de GRADE-methodiek spelen grenzen voor klinische besluitvorming een belangrijke rol (Hultcrantz, 2017). Dit zijn de grenzen die bij overschrijding aanleiding zouden geven tot

een aanpassing van de aanbeveling. Om de grenzen voor klinische besluitvorming te bepalen moeten alle relevante uitkomstmaten en overwegingen worden meegewogen. De grenzen voor klinische besluitvorming zijn daarmee niet één op één vergelijkbaar met het minimaal klinisch relevant verschil (Minimal Clinically Important Difference, MCID). Met name in situaties waarin een interventie geen belangrijke nadelen heeft en de kosten relatief laag zijn, kan de grens voor klinische besluitvorming met betrekking tot de effectiviteit van de interventie bij een lagere waarde (dichter bij het nuleffect) liggen dan de MCID (Hultcrantz, 2017).

Overwegingen (van bewijs naar aanbeveling)

Om te komen tot een aanbeveling zijn naast (de kwaliteit van) het wetenschappelijke bewijs ook andere aspecten belangrijk en worden meegewogen, zoals aanvullende argumenten uit bijvoorbeeld de biomechanica of fysiologie, waarden en voorkeuren van patiënten, kosten (middelenbeslag), aanvaardbaarheid, haalbaarheid en implementatie. Deze aspecten zijn systematisch vermeld en beoordeeld (gewogen) onder het kopje 'Overwegingen' en kunnen (mede) gebaseerd zijn op expert opinion. Hierbij is gebruik gemaakt van een gestructureerd format gebaseerd op het evidence-to-decision framework van de internationale GRADE Working Group (Alonso-Coello, 2016a; Alonso-Coello 2016b). Dit evidence-to-decision framework is een integraal onderdeel van de GRADE methodiek.

Formuleren van aanbevelingen

De aanbevelingen geven antwoord op de uitgangsvraag en zijn gebaseerd op het beschikbare wetenschappelijke bewijs en de belangrijkste overwegingen, en een weging van de gunstige en ongunstige effecten van de relevante interventies. De kracht van het wetenschappelijk bewijs en het gewicht dat door de werkgroep wordt toegekend aan de overwegingen, bepalen samen de sterkte van de aanbeveling. Conform de GRADE-methodiek sluit een lage bewijskracht van conclusies in de systematische literatuuranalyse een sterke aanbeveling niet a priori uit, en zijn bij een hoge bewijskracht ook zwakke aanbevelingen mogelijk (Agoritsas, 2017; Neumann, 2016). De sterkte van de aanbeveling wordt altijd bepaald door weging van alle relevante argumenten tezamen. De werkgroep heeft bij elke aanbeveling opgenomen hoe zij tot de richting en sterkte van de aanbeveling zijn gekomen.

In de GRADE-methodiek wordt onderscheid gemaakt tussen sterke en zwakke (of conditionele) aanbevelingen. De sterkte van een aanbeveling verwijst naar de mate van zekerheid dat de voordelen van de interventie opwegen tegen de nadelen (of vice versa), gezien over het hele spectrum van patiënten waarvoor de aanbeveling is bedoeld. De sterkte van een aanbeveling heeft duidelijke implicaties voor patiënten, behandelaars en beleidsmakers (zie onderstaande tabel). Een aanbeveling is geen dictaat, zelfs een sterke aanbeveling gebaseerd op bewijs van hoge kwaliteit (GRADE gradering HOOG) zal niet altijd van toepassing zijn, onder alle mogelijke omstandigheden en voor elke individuele patiënt.

Implicaties van sterke en zwakke aanbevelingen voor verschillende richtlijngebruikers		
	Sterke aanbeveling	*Zwakke (conditionele) aanbeveling*
Voor patiënten	De meeste patiënten zouden de aanbevolen interventie of aanpak kiezen en slechts een klein aantal niet.	Een aanzienlijk deel van de patiënten zouden de aanbevolen interventie of aanpak kiezen, maar veel patiënten ook niet.
Voor behandelaars	De meeste patiënten zouden de aanbevolen interventie of aanpak moeten ontvangen.	Er zijn meerdere geschikte interventies of aanpakken. De patiënt moet worden ondersteund

		bij de keuze voor de interventie of aanpak die het beste aansluit bij zijn of haar waarden en voorkeuren.
Voor beleidsmakers	De aanbevolen interventie of aanpak kan worden gezien als standaardbeleid.	Beleidsbepaling vereist uitvoerige discussie met betrokkenheid van veel stakeholders. Er is een grotere kans op lokale beleidsverschillen.

Organisatie van zorg

In de knelpuntenanalyse en bij de ontwikkeling van de richtlijnmodule is expliciet aandacht geweest voor de organisatie van zorg: alle aspecten die randvoorwaardelijk zijn voor het verlenen van zorg (zoals coördinatie, communicatie, (financiële) middelen, mankracht en infrastructuur). Randvoorwaarden die relevant zijn voor het beantwoorden van deze specifieke uitgangsvraag zijn genoemd bij de overwegingen. Meer algemene, overkoepelende, of bijkomende aspecten van de organisatie van zorg worden behandeld in de module Organisatie van zorg.

Commentaar- en autorisatiefase

De conceptrichtlijnmodule werd aan de betrokken (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd ter commentaar. De commentaren werden verzameld en besproken met de werkgroep. Naar aanleiding van de commentaren werd de conceptrichtlijnmodule aangepast en definitief vastgesteld door de werkgroep. De definitieve richtlijnmodule werd aan de deelnemende (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd voor autorisatie en door hen geautoriseerd dan wel geaccordeerd [pending].

Literatuur

Agoritsas T, Merglen A, Heen AF, Kristiansen A, Neumann I, Brito JP, Brignardello-Petersen R, Alexander PE, Rind DM, Vandvik PO, Guyatt GH. UpToDate adherence to GRADE criteria for strong recommendations: an analytical survey. BMJ Open. 2017 Nov 16;7(11):e018593. doi: 10.1136/bmjopen-2017-018593. PubMed PMID: 29150475; PubMed Central PMCID: PMC5701989.

Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Rada G, Rosenbaum S, Morelli A, Guyatt GH, Oxman AD; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ. 2016 Jun 28;353:i2016. doi: 10.1136/bmj.i2016. PubMed PMID: 27353417.

Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Vandvik PO, Meerpohl J, Guyatt GH, Schünemann HJ; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ. 2016 Jun 30;353:i2089. doi: 10.1136/bmj.i2089. PubMed PMID: 27365494.

Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, Fervers B, Graham ID, Grimshaw J, Hanna SE, Littlejohns P, Makarski J, Zitzelsberger L; AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010 Dec 14;182(18):E839-42. doi: 10.1503/cmaj.090449. Epub 2010 Jul 5. Review. PubMed PMID: 20603348; PubMed Central PMCID: PMC3001530.

Hultcrantz M, Rind D, Akl EA, Treweek S, Mustafa RA, Iorio A, Alper BS, Meerpohl JJ, Murad MH, Ansari MT, Katikireddi SV, Östlund P, Tranæus S, Christensen R, Gartlehner G, Brozek J, Izcovich A, Schünemann H, Guyatt G. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol. 2017 Jul;87:4-13. doi:

10.1016/j.jclinepi.2017.05.006. Epub 2017 May 18. PubMed PMID: 28529184; PubMed Central PMCID: PMC6542664.

Medisch Specialistische Richtlijnen 2.0 (2012). Adviescommissie Richtlijnen van de Raad Kwalitieit.
http://richtlijnendatabase.nl/over_deze_site/over_richtlijnontwikkeling.html

Neumann I, Santesso N, Akl EA, Rind DM, Vandvik PO, Alonso-Coello P, Agoritsas T, Mustafa RA, Alexander PE, Schünemann H, Guyatt GH. A guide for health professionals to interpret and use recommendations in guidelines developed with the GRADE approach. J Clin Epidemiol. 2016 Apr;72:45-55. doi: 10.1016/j.jclinepi.2015.11.017. Epub 2016 Jan 6. Review. PubMed PMID: 26772609.

Schünemann H, Brożek J, Guyatt G, et al. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from http://gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html.

Module 1 Diagnostiek VTE

Autorisatie en geldigheid

Autorisatiedatum:	*pending*
Eerstvolgende beoordeling actualiteit	volgende cyclus binnen het cluster Antitrombotisch beleid
Geautoriseerd door:	*pending*
Belangrijkste wijzigingen t.o.v. vorige versie:	n.v.t., het betreft een nieuwe module
Herbevestiging:	n.v.t.
Regiehouder:	Nederlandse Internisten Vereniging

Uitgangsvraag

Wat is de optimale diagnostiek van volwassen patiënten met een klinische verdenking van een Veneuze Trombo-Embolie (VTE)?

Inleiding

Het is routine geworden om het diagnostisch proces van een vermoeden op diepe veneuze trombose (DVT) of longembolie (PE) te beginnen met een klinische beslisregel en een D-dimeer test. Op basis van die twee testen wordt vervolgens selectief beeldvorming toegepast om een diagnose uit te sluiten of aan te tonen. Dit betekent dat een deel van de patiënten met een negatieve uitslag van beslisregel en D-dimeer test geen verder duur en tijdsintensief diagnostisch vervolgonderzoek in de vorm van radiologische beeldvorming hoeft te ondergaan. Het is belangrijk om na te gaan of de accuratesse van de klinische beslisregels in combinatie met D-dimeer testen goed genoeg is om dit te kunnen doen. Belangrijk is dat een negatieve testuitkomst de diagnose uitsluit, dus een hoge negatieve voorspellende waarde (NPV) heeft.

Search and select

A systematic review of the literature was performed to answer the following two questions:

Subquestion 1: What is the safety and efficiency of diagnostic algorithms consisting of a clinical decision rule, D-dimer and imaging in patients with a suspected first episode or a recurrent episode of deep vein thrombosis (DVT)?

P	**(Patients)**	adult patients with suspected first episode or relapsed DVT
I	**(Index test**)	positive outcome clinical decision rule + d-dimer
C	**(Comparison)**	negative outcome clinical decision rule + d-dimer
R	**(Reference)**	number of patients with DVT based on compression ultrasonography/Magnetic Resonance Direct Thrombus Imaging or during 3 months follow up
O	**(Outcomes)**	negative predictive value, sensitivity, specificity
T/S	**(Timing/setting)**	hospital

Subquestion 2: What is the safety and efficiency of diagnostic algorithms consisting of a clinical decision rule, D-dimer and imaging in patients with a suspected first episode or a recurrent episode of recurrent pulmonary embolism (PE)?

P	**(Patients)**	adult patients with suspected first episode or relapsed pulmonary embolism
I	**(Index test)**	positive outcome clinical decision rule + d-dimer

C	**(Comparison)**	negative outcome clinical decision rule + d-dimer
R	**(Reference)**	number of patients with pulmonary embolism based on CTPA, V-Q long scan of SPECT, or during 3 months follow up
O	**(Outcomes)**	negative predictive value, sensitivity, specificity
T/S	**(Timing/setting)**	hospital

Relevant outcome measures

The guideline development group considered negative predictive value (safety) as a critical outcome measure for decision making, and sensitivity and specificity as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

Per outcome, the working group defined the following minimal clinically important differences:

- Negative predictive value (NPV) of ≥97%
- Sensitivity of ≥90%
- Efficiency/specificity as high as possible

With respect to the NPV, a prevalence dependent cut-off value was applied in the discussion and recommendations, as recommended by the International Society on Thrombosis and Haemostasis (Dronkers, 2021). The combination of a clinical decision rule and a D-dimer test cannot confirm the diagnosis, and follow-up imaging is necessary to do this. Therefore the working group did not a priori define a minimal clinically important difference for efficiency/specificity.

For DVT, the NPV of a diagnostic algorithm in excluding proximal DVT was analysed (distal DVT was not taken into account). Proximal DVT is defined as a DVT at the level of the popliteal vein and/or located more proximal.

Search and select (Methods)

The databases Embase and Ovid/Medline were searched with relevant search terms from 2009 until 15-12-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 508 hits. Studies were selected based on the following criteria:

- systematic reviews (searched in at least two databases, and detailed search strategy, risk of bias assessment and results of individual studies available), randomized controlled trials, or observational comparative studies,
- full-text English language publication,
- adult patients with suspected first episode or relapsed pulmonary embolism or DVT, and
- studies according to the PICO.

30 studies were initially selected based on title and abstract screening. After reading the full text, 26 studies were excluded (see the table with reasons for exclusion under the tab Methods), and four studies were included.

Results

Four studies were included in the analysis of the literature. For DVT, two IPD meta-analyses were included. The second IPD meta-analysis by Parpia (2019) is a follow-up that reported on additional outcome measures (sensitivity and specificity) in a subsample of the first IPD meta-analysis (Geersing, 2014). For pulmonary embolism, two systematic reviews and

individual-patient data (IPD) meta-analysis were included (Geersing, 2022; Stals 2022). Both studies report comparable results based on similar measures in an almost identical dataset. The two studies complement each other for the outcomes and subgroup analyses of interest for this guideline. Geersing (2022) was used as the main study since it also reports sensitivity and specificity, thus encompassing all outcomes of interest. From Stals (2022), 2 subgroup analyses are included, i.e. patients with cancer and those with suspected recurrent VTE . Important study characteristics and results of the four studies are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Part I: Deep vein thrombosis (DVT)

Geersing (2014) performed an IPD meta-analysis to assess the safety of an unlikely score on the Wells rule combined with a negative D-dimer test result for excluding DVT in outpatients. The authors report the diagnostic failure rate and efficiency for different settings, including in the secondary/hospital setting. Studies were included if they (1) included outpatients with clinically suspected DVT, (2) assessed variables to calculate the Wells rule, (3) had a prospective follow-up design, and (4) applied a reference standard of imaging and/or clinical follow-up for three months in those in whom DVT was ruled out without imaging. A previous meta-analysis and literature search to update the results from 2006 yielded 13 studies that fulfilled these criteria, resulting in a sample size of 10,002 patients. A DVT diagnosis was present in 1864 (19%) of all patients; the prevalence varied from 5% to 39% between studies. 62% were female and the median age was 59 years. The subgroup analysis for hospital care for studies with D-dimer data included 4,511 patients from 5 studies with a prevalence varying from 16% to 39%. For D-dimer testing both qualitative and quantitative assays were used, with a mix of thresholds for the quantitative assays (the threshold used within the study). The IPD meta-analysis was performed on imputed data with multilevel logistic regression models involving a random intercept for study (to account for the clustering of patients within studies). Two outcome measures were reported by the authors: (1) diagnostic failure rate: the mean predicted probability of DVT in patients with a score ≤1 on the Wells rule combined with a negative D-dimer test result and (2) efficiency: the proportion of individuals classified by the strategy as DVT considered excluded without imaging. Thus, the failure rate is similar to a false negative test result (i.e. 1 minus negative predictive value) and efficiency is similar to the true negatives plus false negatives as proportion of the total study population.

Parpia (2019) performed an IPD meta-analysis to assess the accuracy of different clinical decision rules (CDRs) for excluding DVT in outpatients. The CDRs investigated were Wells score ≤ 1 combined with either a fixed (500 µg/L) or age-adjusted D-dimer thresholds (age x 10 µg/L in patients aged >50 years). This study used three studies that quantitatively measured D-dimer levels from the IPD database established by Geersing (2014) plus one additional study performed by their group. Studies were included if they (1) included outpatients with clinically suspected DVT, (2) assessed variables to calculate Wells rule, (3) had a prospective follow-up design, (4) applied a reference standard of imaging and/or clinical follow-up for three months in those in whom DVT was ruled out without imaging at initial presentation and (5) used quantitative D-dimer assays. Four studies with 3,368 patients fulfilled these criteria. 814 patients with a Wells score of >2 were excluded as D-dimer is not recommended to exclude DVT in these patients. Ultimately, 2554 patients were included in the analysis. A DVT diagnosis was present in 12% of all patients; this prevalence varied from 5% to 31% between studies. Distribution of patients in Wells 0 or 1-2 also varied across studies. 64% of all patients were female, the mean age was 59 years and 44% had a

low CPTP. Three studies were performed in the secondary care setting and one study in the primary care setting. The authors performed a two-stage meta-analysis, first obtaining summary estimates for each separate study, and second combining these using a meta-analysis model.

Part II: Pulmonary embolism(PE)

Geersing (2022) performed a systematic review and IPD meta-analysis to examine the use of different CDRs for ruling out acute PE in a variety of healthcare settings. The CDRs investigated were Wells and revised Geneva scores combined with D-dimer interpretations either using a fixed cut-off (using either qualitative or quantitative D-dimer testing), adjusted to pretest probability (PTP), or age-adjusted D-dimer thresholds (age x 10 µg/L in patients aged >50 years), as well as the YEARS algorithm. In the YEARS algorithm the D-dimer threshold depends on clinical pretest probability (CPTP) assessment (as in: higher D-dimer threshold for patients with a low CPTP). For the PTP adjusted D-dimer levels, low probability (Wells score of ≤4 or Geneva score of ≤5) has a D-dimer cut-off of 1000 ng/ml and moderate probability (Wells score of > 4 or Geneva score of ≥6) has a D-dimer cut-off of 500 ng/ml. If PE could not be ruled out based on the combination of CDR and D-dimer testing, a computed tomography pulmonary angiography (CTPA) was ordered to confirm or refute the diagnosis. Studies were included if they (1) included patients with clinically suspected PE, (2) assessed variables to calculate at least 1 of the CDRs of interest, (3) had a prospective follow-up or cross-sectional study design, (4) provided a clear description of the healthcare setting, (5) involved at least 50 patients with confirmed VTE and (6) applied a reference standard of either imaging or a clinical follow-up of at least 1 month in those in whom PE was ruled out at initial presentation without imaging. In addition, studies were excluded if only qualitative D-dimer measurements were performed and patients with only low clinical pretest probability were included. A literature search from 1 January 1995 until 1 November 2021 in MEDLINE yielded 23 studies that fulfilled these criteria, accumulating to 35,248 patients available for analysis. For referred secondary care, the analysis included 14 studies with 17,052 patients and a mean baseline PE prevalence of 20%. This prevalence varied from 14% to 41% between studies. Four outcome measures were reported by the authors: (1) diagnostic failure rate: “the predicted 3-month VTE incidence after exclusion of PE without imaging at baseline”; (2) efficiency: “the proportion of individuals classified by the strategy as PE considered excluded without imaging tests”; (3) sensitivity and (4) specificity. The IPD meta-analysis was performed on imputed data with multilevel logistic regression models involving a random intercept for study (to account for the clustering of patients within studies) for failure rate and efficiency. For sensitivity and specificity, univariate random effects modeling were used due to nonconvergence issues encountered in bivariate random effects modeling.

Stals (2022) performed a systematic review and IPD meta-analysis using the same dataset as the Geersing study described above, to examine the use of different CDRs for ruling out acute PE in important patient subgroups. The CDRs investigated were Wells and revised Geneva scores combined with fixed (500 µg/L) and age-adjusted D-dimer thresholds (age x 10 µg/L in patients aged >50 years), as well as the YEARS algorithm. In the YEARS algorithm the D-dimer threshold depends on clinical pretest probability (CPTP) assessment (as in: higher D-dimer threshold for patients with a low CPTP). . If PE could not be ruled out based on the combination of CDR and D-dimer testing, a computed tomography pulmonary angiography (CTPA) was ordered to confirm or refute the diagnosis. Studies were included if they (1) included patients with clinically suspected PE, (2) assessed variables to calculate at least 1 of the CDRs of interest, (3) had a prospective follow-up or cross-sectional study design and (4) applied a reference standard of either imaging or clinical follow-up in those in

whom PE was ruled out without imaging. In addition, studies were excluded if only qualitative D-dimer measurements were performed and patients with only low clinical pretest probability were included. A literature search from 1 January 1995 until 1 January 2021 in MEDLINE yielded 16 studies that fulfilled these criteria, accumulating to 20 553 patients available for analysis. A VTE diagnosis was present in 3932 (19%) of all patients; this prevalence varied from 7.4% to 41% between studies. The IPD meta-analysis was performed on imputed data with multilevel logistic regression models with a random intercept for study (to account for the clustering of patients within studies). Two outcome measures were reported by the authors: (1) diagnostic failure rate: "the predicted 3-month VTE incidence after exclusion of PE without imaging at baseline." and (2) efficiency: "the proportion of individuals classified by the strategy as PE considered excluded without imaging tests". The authors performed pre-defined subgroup analyses for active cancer (as defined in the original studies) and history of VTE.

Results

Part I: Deep vein thrombosis (DVT)

Negative predictive value

In the study of Geersing (2014), 4,511 patients were analysed in an IPD meta-analysis to assess the accuracy of an unlikely score on the Wells rule (≤1) combined with a negative D-dimer test result for excluding DVT .
Enough information was available to post hoc estimate the negative predictive value (NPV) as following: NPV = 1 – failure rate. Results are shown in Table 1.

In the study of Parpia (2019), 2,554 patients with low (≤0) or moderate (1-2) Wells scores were analysed in an IPD meta-analysis to assess the accuracy of different CDRs for excluding DVT in hospital and primary care outpatients. Restricting to a population with low or moderate Wells-pre-test probability means a lower prevalence of DVT, which can lead to higher NPV estimates. Results are shown in Table 1.

Sensitivity and specificity

In the study of Parpia (2019), 2,554 patients with low (≤0) or moderate (1-2) Wells scores were analysed in an IPD meta-analysis to assess the accuracy of different CDRs for excluding DVT in hospital and primary care outpatients. Results are shown in Table 1.

Table 1. Failure rate, efficiency, negative predictive value (NPV), sensitivity and specificity for an unlikely score on the Wells rule combined with a negative D-dimer test result for ruling out DVT (Geersing, 2014 and Parpia, 2019).

Study	Clinical decision rule	N	Prevalence DVT	Failure rate (% (95%CI))	Efficiency (% (95%CI))	NPV (% (95%CI))	Sensitivity (% (95%CI))	Specificity (% (95%CI))
Geersing (2014)	Wells score (≤1) and negative D-dimer test	4511	26%	0.9 (0.0 to 1.9)	23.1% (12.8 to 38.3)	99.1**	-	-
Parpia (2019)*	Wells score (≤0) and D-dimer <500 µg/L	2554	12%	0.2**	38.9 (29.1 to 48.7)	99.8 (99.5 to 100)	99.0 (97.8 to 100.0)	45.2 (39.6 to 50.9)
	Wells score (≤0) and age- adjusted D-dimer (age x 10 µg/L for >50 years)	2554	12%	0.3**	47.4 (35.3 to 59.3)	99.7 (99.4 to 100.0)	98.0 (96.3 to 99.5)	54.7 (48.3 to 61.2)

*** Parpia (2019) only included patients with low or moderate clinical pre-test probability on the Wells score. The lower prevalence of DVT can lead to higher NPV estimates.**
**** Enough information was available to post hoc estimate the negative predictive value (NPV) or failure rate as following: NPV = 1 - failure rate.**

Part II: Pulmonary embolism (PE)

Negative predictive value overall

In the study of Geersing (2022), 17,052 patients were analysed in an individual patient data meta-analysis to examine the use of different CDRs for ruling out acute PE in referred secondary care. Enough information was available to post hoc estimate the negative predictive value (NPV) for different CDRs as following: NPV = 1 - failure rate. Results are shown in Table 2. Using the Wells score with PTP adjusted D-dimer resulted in a NPV of 96.9, which is just below the minimally clinically relevant threshold of 97%.

Table 2. Failure rate, efficiency, negative predictive value (NPV), sensitivity and specificity for different clinical decision rules for ruling out acute PE (Geersing, 2022).

Clinical decision rule	N	Failure rate (% (95%CI))	Efficiency (% (95%CI))	NPV (%)*	Sensitivity (% (95%CI))	Specificity(% (95%CI))
Wells score with qualitative/fixed D-dimer threshold <500 µg/L	15 531	0.75 (0.50 to 1.13)	29.57 (25.39 to 34.12)	99.3	98.38 (95.87 to 99.41)	36.89 (32.53 to 41.47)
Wells score with fixed D-dimer threshold <500 µg/L	15 114	0.32 (0.17 to 0.60)	27.77 (23.05 to 33.03)	99.7	99.59 (99.10 to 99.82)	35.21 (30.19 to 40.57)
Wells score with age-adjusted D-dimer threshold (age x 10 µg/L for >50 years)	15 114	0.65 (0.43 to 0.99)	32.91 (27.85 to 38.39)	99.4	98.93 (98.15 to 99.39)	41.58 (36.42 to 46.93)
Wells score with PTP adjusted D-dimer	15 114	3.06 (2.47 to 3.78)	48.78 (43.64 to 53.94)	96.9	93.25 (91.91 to 94.38)	60.80 (56.24 to 65.19)
Revised Geneva score with qualitative/fixed D-dimer threshold <500 µg/L	13 245	1.17 (0.79 to 1.74)	30.46 (26.75 to 34.44)	98.8	97.75 (93.86 to 99.27)	39.25 (34.57 to 44.14)
Revised Geneva score with fixed D-dimer threshold <500 µg/L	12 828	0.37 (0.19 to 0.74)	28.77 (26.20 to 31.48)	99.6	99.53 (98.88 to 99.80)	37.23 (34.00 to 40.57)
Revised Geneva score with age-adjusted D-dimer threshold (age x 10 µg/L for >50 years)	12 828	0.81 (0.51 to 1.27)	35.25 (32.76 to 37.82)	99.2	98.51 (97.37 to 99.16)	45.27 (42.63 to 47.95)
Revised Geneva score with PTP adjusted D-dimer	12 828	2.95 (2.34 to 3.71)	43.02 (38.28 to 47.31)	97.1	98.51 (97.37 to 99.16)	45.27 (42.63 to 47.95)
YEARS algorithm (D-dimer threshold, 1000 µg/L if 0 YEARS items and D-dimer 500 µg/L if 1–3 YEARS items)	15 114	2.10 (1.59 to 2.75)	43.38 (38.86 to 48.01)	97.9	96.15 (94.87 to 97.12)	54.39 (49.87 to 58.85)

*** Enough information was available to post hoc estimate the negative predictive value (NPV) for different CDRs as following: NPV = 1 - failure rate.**

Negative predictive value in two subgroup analyses

Two subgroups were analysed: patients with cancer and history of VTE. These subgroups were arbitrarily chosen because their patient characteristics may influence the performance of the diagnostic algorithms. In particular, the prevalence of VTE is often higher, and as a result the NPV is lower. As a result, certain algorithms may be less safe. In the study of **Stals (2022)**, 20,553 patients were analysed in an individual patient data meta-analysis to examine the use of different CDRs for ruling out acute PE. Sufficient information was available to post-hoc estimate the negative predictive value (NPV) for different CDRs as follows: NPV = 1 - failure rate. Results for the subgroup analyses for active cancer are shown in Table 3. Results for the subgroup analyses for history of VTE are shown in Table 4. In cancer patients

and patients with a history of VTE, the NPV is slightly below the minimally clinically relevant threshold of 97%, when using the YEARS algorithm. However, as the baseline prevalence of PE is considerably higher in those specific subgroups and the sensitivity was above 90% (data not reported in Stals (2022) but retrieved by personal communication), these NPV's (96.6 and 96.5, respectively) are within the acceptable range (Dronkers, 2021).

Table 3. Failure rate, efficiency, and negative predictive value (NPV) for different clinical decision rules for ruling out acute PE in patients with and without cancer (Stals, 2022).

Clinical decision rule	No cancer (N = 18,334)			Cancer (N = 2,219)		
	Failure rate (% (95%CI))	**Efficiency (% (95%CI))**	**NPV***	**Failure rate (% (95%CI))**	**Efficiency (% (95%CI))**	**NPV***
Wells score with fixed D-dimer threshold (500 µg/L)	0.36 (0.14–0.94)	28 (12–53)	99.6	No failures	9.6 (3.4–24)	100
Wells score with age-adjusted D-dimer threshold (age x 10 µg/L for >50 years)	0.74 (0.32–1.7)	34 (17–56)	99.3	1.1 (0.25–4.7)	15 (6.2–31)	98.9
Revised Geneva score with fixed D-dimer threshold (500 µg/L)	0.5(0.21–1.4)	33 (15–57)	99.4	1.3 (0.26–6.6)	12 (4.6–27)	98.7
Revised Geneva score with age-adjusted D-dimer threshold (age x 10 µg/L for >50 years)	1 (0.43–2.5)	39 (22–60)	99	2.5 (0.73–8.0)	18 (8.5–34)	97.5
YEARS algorithm (D-dimer threshold, 1000 µg/L if 0 YEARS items and D-dimer 500 µg/L if 1–3 YEARS items)	1.7 (0.74–4.0)	44 (24–66)	98.3	3.4 (1.2–9.0)	21 (9.6–39)	96.6

*** Enough information was available to post hoc estimate the negative predictive value (NPV) for different CDRs as following: NPV = 1 -failure rate.**

Table 4. Failure rate, efficiency, and negative predictive value (NPV) for different clinical decision rules for ruling out acute PE in patients with and without a history of VTE (Stals, 2022).

Clinical decision rule	No history of VTE (N = 17611)			History of VTE (N = 2942)		
	Failure rate (% (95%CI))	**Efficiency (% (95%CI))**	**NPV***	**Failure rate (% (95%CI))**	**Efficiency (% (95%CI))**	**NPV***
Wells score with fixed D-dimer threshold (500 µg/L)	0.33 (0.14–0.77)	30 (13–55)	99.7	0.48 (0.07–3.4)	12 (4.5–28)	99.5
Wells score with age-adjusted D-dimer threshold (age x 10 µg/L for >50 years)	0.70 (0.35–1.4)	36 (19–57)	99.3	1.0 (0.23–4.3)	15 (6.7–30)	99
Revised Geneva score with fixed D-dimer threshold (500 µg/L)	0.48 (0.21–1.1)	33 (15–58)	99.5	1.2 (0.39–3.3)	21 (8.6–43)	98.8
Revised Geneva score with age-adjusted D-dimer threshold (age x 10 µg/L for >50 years)	0.87 (0.43–1.7)	39 (21–60)	99.1	2.5 (1.1–5.7)	27 (14–47)	97.5
YEARS algorithm (D-dimer threshold, 1000 µg/L if 0 YEARS items and D-dimer 500 µg/L if 1–3 YEARS items)	1.5 (0.77–2.9)	44 (24–66)	98.5	3.5 (1.7–7.2)	32 (16–54)	96.5

*** Enough information was available to post hoc estimate the negative predictive value (NPV) for different CDRs as following: NPV = 1 - failure rate.**

Sensitivity and specificity

In the study of Geersing (2022), 17,052 patients were analysed in an individual patient data meta-analysis to examine the use of different CDRs for ruling out acute PE in referred secondary care. Results are shown in Table 2.

Level of evidence of the literature

Part I: Deep vein thrombosis (DVT)

The evidence was derived from one systematic review with an IPD meta-analysis and a second follow-up IPD meta-analysis. The level of evidence for all reported outcome measures started at 'high quality'.

Negative predictive value

The level of evidence regarding the critical outcome measure negative predictive value was downgraded by two levels to low, because of: study limitations including differences in the index test (mix qualitative and quantitative D-dimer assays with different thresholds), heterogeneity in DVT prevalence, lack of blinding of the reference standard assessor, only point estimates for NPV could be post hoc estimated from the reported information, and exclusion of patients with a Wells score >2 in the study of Parpia et al (2019) (-2 risk of bias).

Sensitivity and specificity

The level of evidence regarding the important outcome measure sensitivity was downgraded by two levels to low because of: study limitations including different settings (one of four studies included in meta-analysis in the primary care setting), heterogeneity in DVT prevalence and distribution of patients in Wells 0 or 1-2, lack of blinding of the reference standard assessor, and exclusion of patients with a Wells score >2 (-2 risk of bias).

The level of evidence regarding the important outcome measure specificity was downgraded by two levels to low because of: study limitations including different settings (primary and secondary care), heterogeneity in DVT prevalence and distribution of patients in Wells 0 or 1-2, lack of blinding of the reference standard assessor, and exclusion of patients with a Wells score >2 (-2 risk of bias).

Part II: Pulmonary embolism

The evidence was derived from two systematic reviews and IPD meta-analyses. The level of evidence for all reported outcome measures started at 'high quality'.

Negative predictive value overall

For the main results, the level of evidence regarding the critical outcome measure negative predictive value was downgraded by two levels to low because of: study limitations including heterogeneity in prevalence, only point estimates for NPV could be post hoc estimated from the reported information, unclear reference standard, and index test issues (-2 risk of bias).

Negative predictive value subgroup analyses

For the subgroup results, the level of evidence regarding the critical outcome measure negative predictive value was downgraded by two levels to low because of: study limitations including heterogeneity in prevalence, only point estimates for NPV could be post hoc estimated from the reported information, unclear reference standard, and index test issues (-2 risk of bias).

Sensitivity and specificity

The level of evidence regarding the important outcome measure sensitivity was downgraded by one level to moderate because of: study limitations including heterogeneity in prevalence, unclear reference standard, and index test issues (-1 risk of bias).

The level of evidence regarding the important outcome measure specificity was downgraded by one level to moderate because of: study limitations including heterogeneity in prevalence, unclear reference standard, and index test issues (-1 risk of bias).

Conclusions

Part I: Deep vein thrombosis (DVT)

Negative predictive value

Low GRADE	The evidence suggests that clinical decision rules plus d-dimer testing may have a high negative predictive value in patients suspected of having deep vein thrombosis in the referred secondary care setting. *Source: Geersing, 2014; Parpia, 2019*

Specificity and sensitivity

Low GRADE	The evidence suggests that clinical decision rules plus d-dimer testing may be sensitive but not specific in diagnosing patients suspected of having deep vein thrombosis. *Source: Parpia, 2019*

Part II: Pulmonary embolism (PE)

Negative predictive value

Overall

Low GRADE	The evidence suggests that clinical decision rules plus d-dimer testing may have a high negative predictive value in patients suspected of having pulmonary embolism in the referred secondary care setting. *Source: Geersing 2022*

Subgroups

Low GRADE	In patients with cancer or a history of VTE, the evidence suggests that clinical decision rules plus d-dimer testing may have a lower negative predictive value for patients suspected of having pulmonary embolism in the hospital setting than the patients without cancer and/or a history of VTE. *Source: Stals 2022*

Specificity and sensitivity

Moderate GRADE	The evidence suggests that clinical decision rules plus d-dimer testing likely are sensitive but not specific in diagnosing patients suspected of having pulmonary embolism in the referred secondary care setting. *Source: Geersing 2022*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

DVT

Bij patiënten met een klinische verdenking op DVT hebben klinische beslisregels in combinatie met een D-dimeer test mogelijk een hoge negatief voorspellende waarde (NPV) en hoge sensitiviteit om een proximale DVT uit te sluiten, maar een lage specificiteit om de diagnose DVT vast te stellen. De bewijskracht hiervoor is laag door de verschillende prevalenties (12% in Parpia (2019) en 26% in Geersing (2014)), toegepaste referentiestandaarden en indextesten (mix kwalitatieve en kwantitatieve D-dimeer assay) in de studies. Voor de NPV kon per diagnostische strategie alleen een puntschatting worden berekend, waardoor informatie over de spreiding en heterogeniteit niet te bepalen was. De hoge sensitiviteit en NPV betekent dat patiënten met een negatieve uitslag geen diagnostisch vervolgonderzoek (echografie) hoeven te ondergaan. De lagere specificiteit betekent dat fout positieven kunnen optreden als alleen klinische beslisregels in combinatie met een D-dimeer test wordt gehanteerd om een DVT aan te tonen, dus dat vervolgonderzoek vereist is om een diagnose te stellen.

Twee-punts compressie-echografie heeft een hoge sensitiviteit (90,1% (95% BI: 86,5 tot 92,8) om een eerste episode van proximale DVT uit te sluiten en een hoge specificiteit 98,5% (95% BI 97,6 tot 99,1%) om een eerste episode van proximale DVT aan te tonen (Lensing, 1989 en Bhatt, 2020). Dit is dus het beeldvormend vervolgonderzoek van keuze om DVT aan te tonen of uit te sluiten. Omdat 2-punts compressie-echografie veelal laagdrempelig beschikbaar is, steeds meer met point-of-care echomachines uitgevoerd wordt, goedkoop is en geen nadelige effecten op de patiënt heeft, kan ervoor gekozen worden om de stap met de voorafkans bepaling en D-dimeer test over te slaan. Als alternatief kan een zogenaamde complete compressie-echografie worden uitgevoerd. Deze methode is arbeidsintensiever omdat meer veneuze segmenten in het bovenbeen en onderbeen onderzocht moeten worden. Daarnaast is het potentiële probleem van overdiagnostiek van geïsoleerde kuit(spier)vene tromboses waarvan de noodzaak voor behandeling wordt betwijfeld (Bernardi, 2008). De NHG-Standaard kiest daarom voor een 2-punts compressie-echografie (CUS). Indien men kiest om een complete CUS uit te voeren en deze niet beschikbaar is buiten kantooruren kan alsnog een 2-punts compressie-echografie worden uitgevoerd volgens het stroomschema.

Bij klinische verdenking op een recidief DVT is de echografie minder specifiek door het frequent voorkomen van persisterende stolselresten na een eerste DVT. Zo bleek in een retrospectieve studie, dat bij 29 van de 90 patiënten (32%) bij wie een CUS was verricht vanwege een verdenking van een recidief ipsilaterale DVT, de diagnose niet met zekerheid kon worden gesteld door ontbreken van eerder aanwezige CUS uitslagen, met als gevolg dat deze patiënten mogelijk onterecht met langdurige antistolling behandeld werden. (Tan, 2010). De persisterende stolselresten kunnen vaak niet goed onderscheiden worden van een nieuwe DVT-episode, tenzij er een uitgangsechografie aanwezig is die aantoont dat een stolsel is ontstaan in een nieuw veneus segment, of dat de comprimeerbaarheid van het vat met tenminste 2-4 mm is afgenomen. Het maken van een uitgangscompressie-echografie in alle patiënten die stoppen met antistolling na een eerste DVT in de Nederlandse situatie is echter niet kosteneffectief gebleken (de Jong, 2023). Uit onderzoek blijkt dat ‘MR direct thrombus imaging’ (MRDTI) een vers stolsel kan onderscheiden van stromend bloed of een chronisch reststolsel, door de metabole omzetting van hemoglobine in methemoglobine (Tan, 2014 en van Dam, 2020). Indien compressie echografie geen zekerheid geeft, kan MRDTI worden toegepast om een finale diagnose te stellen. In de Nederlandse situatie is aangetoond dat het gebruik van deze techniek kosteneffectief is (van Dam, 2021) . De MRDTI kan vanaf een half jaar na de index DVT diagnose gebruikt worden (voor die tijd kan de MRDTI nog positief zijn), en wordt het best ingezet in de eerste dagen tot twee weken het na ontstaan van de symptomen (van Dam, 2020).

Longembolie

Bij patiënten met een klinische verdenking op een longembolie op de spoedeisende hulp hebben klinische beslisregels in combinatie met een D-dimeer test mogelijk een hoge negatief voorspellende waarde en hoge sensitiviteit voor het uitsluiten, maar een lage specificiteit om de diagnose longembolie vast te stellen. Het YEARS-algoritme is een veilig, efficiënt en kosteneffectief diagnostisch algoritme (Van der Pol, 2018). In subgroep analyses is de NPV lager in patiënten met kanker of een verleden van eerder doorgemaakte VTE. De bewijskracht hiervoor is laag door verschillen in prevalentie, de referentiestandaard en gebruikte indextest in de studies. Voor de NPV kon per diagnostische strategie alleen een puntschatting worden berekend, waardoor informatie over de spreiding en heterogeniteit niet te bepalen was. Het YEARS-algoritme is eenvoudig te gebruiken in de dagelijkse praktijk en wordt in Nederlandse ziekenhuizen veel toegepast. Ook worden juist in jongere patiënten CT-scans voorkomen, in tegenstelling tot de leeftijdsafhankelijke D-dimeer afkapwaarde. Om deze redenen verdient dit algoritme de voorkeur.

De hoge sensitiviteit en NPV betekent dat patiënten met een negatieve uitslag geen diagnostisch vervolgonderzoek (CT-scan) hoeven te ondergaan. De lagere specificiteit betekent dat fout positieven kunnen optreden als alleen klinische beslisregels in combinatie met een D-dimeer test wordt gehanteerd om een longembolie vast te stellen, dus dat vervolgonderzoek vereist is om een diagnose te stellen. De interpretatie van de hogere incidentie van fout-negatieve uitslagen bij patiënten met een voorgeschiedenis van VTE en kanker is complex. Allereerst is de achtergrond incidentie van (nieuwe) VTE in deze patiëntengroep duidelijk hoger dan in personen zonder deze voorgeschiedenis. Dat blijkt ook uit de observatie dat de incidentie van een fout-negatieve CT-uitslag ook hoger is bij deze patiënten (Stals, 2022 en van der Pol, 2018). Voor de berekening van de proportie van fout-negatieve uitslagen wordt gekeken in een periode van drie maanden, waarbij het de vraag is of een nieuwe VTE na twee maanden follow-up daadwerkelijk een gemiste diagnose is, of een nieuwe episode. De hoogste proportie van fout-negatieve uitslagen wordt gevonden in de meer recent ontworpen diagnostische algoritmes zoals YEARS. Dat wordt mogelijk voor een deel verklaard door een werkelijk hoger aantal gemiste diagnoses omdat het aantal CT-scans dat wordt gemaakt veel lager ligt, maar ook omdat een deel van de gemiste diagnoses kleine, subsegmentele longembolieën betreffen, waarvan de relevantie onduidelijk is (van der Pol, 2018). Het is dus de vraag of dit geen overdiagnostiek betreft, en het werkelijk relevante diagnostische missers zijn. In studies, waarin de nieuwe algoritmes daadwerkelijk zijn toegepast, was er geen belangrijk signaal van een opvallend hoog aantal gemiste diagnoses als op basis van YEARS de diagnose zonder beeldvorming was uitgesloten. Een laatste argument is dat, vooral in de groep patiënten met een actieve maligniteit, onverwacht overlijden tijdens de studie frequent voorkwam en in de regel op conservatieve wijze geduid werd als recidief longembolie (Stals, 2022). In algoritmes waar een lagere proportie van patiënten aan een CT-scan wordt onderworpen, neemt het aantal overlijdens - en dus vaak meegetelde diagnostische missers- proportioneel toe in de groep die geen CT-scan kreeg.

CT pulmonalis angiografie (CTPA) heeft een hoge sensitiviteit (83-100%) om zowel een eerste als herhaalde episode van longembolie uit te sluiten en een hoge specificiteit (89-97-%) om zowel een eerste als herhaalde episode van longembolie aan te tonen (Remy-Jardin, 2007). Deze scan is in alle Nederlandse ziekenhuizen laagdrempelig beschikbaar en geldt als eerste keus beeldvormende test bij verdenking longembolie. Het voordeel van CTPA boven nucleair onderzoek (ventilatie-perfusie scan) is het lagere aantal niet-diagnostische uitslagen, de betere mogelijkheid om met deze beeldvorming gelijktijdig een alternatieve diagnose te stellen en de informatie over hartfunctie – rechter-linker ventrikel ratio - die

geëxtraheerd kan worden en prognostische relevantie heeft voor patiënten met een aangetoonde longembolie. Het nadeel van CTPA ten opzichte van nucleair onderzoek is dat er meer ioniserende stralen aan te pas komen, wat voornamelijk bij jongere personen en vrouwen een zorg is. Daarnaast kunnen soms ernstige allergische reacties optreden bij toediening van het contrast. Vanwege deze - en logistieke redenen is het beperken van het aantal CTPA scans een prioriteit. In de afweging over welke diagnostische strategie preferentieel gebruikt wordt, is de efficiëntie van het algoritme dan ook relevant.

In de IPDMA van patiënten met verdenking longembolie zoals in deze module besproken, waren geen zwangere vrouwen geïncludeerd. Een alternatieve diagnostische regel (LEFt) voor zwangere patienten met een klinische verdenking van DVT wordt momenteel prospectief gevalideerd, maar is dus formeel niet inzetbaar in de dagelijkse praktijk. Bij zwangeren met een hoge verdenking op een DVT maar een normale echo moet gedacht worden aan een geïsoleerde bekkenvene trombose. Aanwijzingen daarvoor kunnen gevonden worden met doppler echografie. Ook de MRDTI scan is uitermate geschikt voor het stellen van deze diagnose omdat er geen contrast voor nodig is en niet gepaard gaat met ioniserende straling.
Voor zwangere patiënten met verdenking longembolie geldt dat de diagnostische algoritmen van de niet zwangere patiënten gevolgd kunnen worden (van der Pol, 2019). Voor kinderen gelden andere algoritmen (buiten het bestek van deze module). Bij patiënten met kanker is de kans op een nieuwe diagnose DVT of longembolie na het uitsluiten van een longembolie (zowel middels beslisregel/D-dimeer test als CT-scan) twee tot vier keer hoger dan bij patiënten zonder kanker. Er loopt onderzoek om vast te stellen wat de meerwaarde is van het volgen van het YEARS-algoritme boven direct en alleen een CT-scan in alle patiënten. Patiënten met kanker zijn meegenomen in de studies waarin de diagnostische algoritmes met een beslisregel en D-dimeer test zijn getest. Om die reden en tot deze studie afgerond is, kan de diagnostiek bij hen ook volgens het routine algoritme verlopen.
Patiënten die therapeutische antistolling gebruiken op het moment van verdenking op VTE dienen meteen verwezen te worden voor een beeldvormende test: de D-dimeer test kan door de antistolling een lage waarde geven, waarmee de sensitiviteit en daarmee de NPV ruimschoots buiten de gestelde veiligheidsnorm vallen.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Het belangrijkste doel van het diagnostische traject bij een vermoeden op een VTE is het op veilige wijze uitsluiten dan wel aantonen van een diepe veneuze trombose of een longembolie. Het belangrijkste voordeel van het diagnostisch algoritme is dat in een groot deel van de patiënten geen radiologisch onderzoek nodig is. Bij de diagnostiek van longembolie betekent dit dat er geen CT-scan nodig is (wat gepaard gaat met stralenbelasting), dat de doorlooptijd op de spoedeisende hulp korter is en dat de patiënt sneller duidelijkheid heeft over de diagnose.

Kosten (middelenbeslag)

Er is aangetoond dat het invoeren van het YEARS-algoritme ten opzichte van het gebruik van de Wells-regel en een D-dimeer test met een vaste afkapwaarde resulteert in een kostenbesparing op de Spoedeisende hulp (van der Pol, 2018). Een formele kosteneffectiviteitsanalyse ontbreekt in de literatuur.

Aanvaardbaarheid, haalbaarheid en implementatie

Er is geen kwantitatief of kwalitatief onderzoek gedaan naar de aanvaardbaarheid en haalbaarheid van de diagnostische procedures. Met betrekking tot diagnostische procedures

wordt er in de praktijk altijd een afweging gemaakt tussen veiligheid (het al dan niet missen van een aandoening) en efficiëntie (geen onnodige diagnostische procedures).
De aanbevolen diagnostische algoritmen die besproken worden in deze richtlijn, worden momenteel gebruikt door het grootste deel van de Nederlandse ziekenhuizen. Veel van de studies zijn uitgevoerd in de Nederlandse setting, wat de validiteit van de resultaten voor de Nederlandse setting onderstreept. De werkgroep verwacht daarom geen problemen ten aanzien van de haalbaarheid, aanvaardbaarheid en implementatie.

Aanbevelingen

Aanbeveling-1 DVT

Rationale van de aanbeveling: weging van argumenten voor en tegen de diagnostische procedure

De combinatie van een klinische beslisregel en een D-dimeer test is een eenvoudige, veilige en non-invasieve manier om een proximale DVT uit te sluiten. Het voordeel hiervan is dat deze combinatie van testen aan het bed van de patiënt kan worden uitgevoerd en er geen noodzaak is om beeldvorming te verrichten. Voor het aantonen en het uitsluiten van een DVT bij een patiënt met een hoge klinische waarschijnlijkheid op de aandoening is een compressie-echografie noodzakelijk. Compressie-echografie neemt weinig tijd in beslag en is laagdrempelig beschikbaar.

Voor volwassen patiënten met een verdenking op een eerste DVT:

Pas een gevalideerde klinische beslisregel toe bij patiënten met een klinische verdenking van een DVT. Volg hierbij de stappen uit het stroomschema 'Diagnostiek bij vermoeden op een (recidief) DVT':

1. *Hoge waarschijnlijkheid DVT op basis van klinische beslisregel*

Voer compressie-echografie uit om de aanwezigheid van een proximale DVT aan te tonen dan wel uit te sluiten.

2. *Lage waarschijnlijkheid DVT op basis van klinische beslisregel*

Voer een D-dimeer test uit.

- Indien D-dimeer test > 500 µg/L :Voer compressie-echografie uit om de aanwezigheid van een proximale DVT aan te tonen dan wel uit te sluiten.
- Indien D-dimeer test ≤ 500 µg/L : proximale DVT is uitgesloten

Indien echografie laagdrempelig beschikbaar is: Overweeg om de combinatie klinische beslisregel/D-dimeer test over te slaan en direct een 2-punts compressie-echografie te verrichten om een proximale DVT uit te sluiten of aan te tonen.

Voor volwassen patiënten met een verdenking op een recidief DVT:

Pas een gevalideerde klinische beslisregel toe bij patiënten met een klinische verdenking van een recidief DVT. Volg hierbij de stappen uit het stroomschema 'Diagnostiek bij vermoeden op een (recidief) DVT':

1. *Hoge waarschijnlijkheid DVT op basis van klinische beslisregel*

Voer compressie-echografie uit om de aanwezigheid van een proximale DVT aan te tonen dan wel uit te sluiten. Er is sprake van een recidief proximale DVT in het geval van een

abnormale 2-punts compressie-echografie in een nieuw veneus segment of indien het niet comprimeerbare oude veneuze segment met ≥ 4 mm is toegenomen.

2. *Lage waarschijnlijkheid DVT op basis van klinische beslisregel*

Voer een D-dimeer test uit.

- Indien D-dimeer test > 500 µg/L : Voer compressie-echografie uit om de aanwezigheid van een proximale DVT aan te tonen dan wel uit te sluiten. Er is sprake van een recidief proximale DVT in het geval van een abnormale 2-punts compressie-echografie in een nieuw veneus segment of indien het oude niet comprimeerbare veneuze segment met ≥ 4 mm is toegenomen.
- Indien D-dimeer test ≤ 500 µg/L : proximale DVT uitgesloten

Indien de compressie echografie niet eenduidig is: overweeg om een MRDTI toe te passen teneinde een recidief DVT aan te tonen dan wel uit te sluiten.

Indien echografie laagdrempelig beschikbaar is: Overweeg om de combinatie klinische beslisregel/D-dimeer test over te slaan en direct een 2-punts compressie-echografie te verrichten om een recidief proximale DVT uit te sluiten,- of aan te tonen.

Aanbeveling-2 Longembolie

Rationale van de aanbeveling: weging van argumenten voor en tegen de diagnostische procedure

De combinatie van een klinische beslisregel en een D-dimeer test is een eenvoudige, veilige en non-invasieve manier om een longembolie uit te sluiten indien de klinische waarschijnlijkheid op deze aandoening niet hoog is. Het voordeel hiervan is dat deze combinatie van testen aan het bed van de patient kan worden uitgevoerd en er geen noodzaak is om een imaging test uit te voeren. Voor het aantonen en uitsluiten van een longembolie bij een patiënt met een hoge klinische waarschijnlijkheid op de aandoening is een CTPA noodzakelijk. CTPA is laagdrempelig beschikbaar. De werkgroep adviseert om te overwegen hierbij het YEARS-algoritme te gebruiken. Ondanks een lagere NPV in de subgroepen van patiënten met kanker en patiënten met een VTE in de voorgeschiedenis, is er naar de mening van de werkgroep onvoldoende aanleiding om het YEARS-algoritme niet aan te bevelen in deze groepen.

Sluit een eerste of herhaalde episode van longembolie uit met behulp van een lage klinische voorafkans (vastgesteld met een gevalideerde beslisregel) en een normale D-dimeer test bij patiënten met een verdenking op een longembolie. Overweeg hierbij om het YEARS-algoritme te gebruiken.

Sluit een eerste of herhaalde episode van een longembolie uit of toon een longembolie aan met een CTPA bij patiënten met een hoge klinische waarschijnlijkheid of afwijkende D-dimeer test.

Volg hierbij de stappen uit het stroomschema ‘Diagnostiek bij verdenking op een longembolie’.

Kennislacunes

Wat is de diagnostische waarde van klinische beslisregels in patiënten met kanker met een vermoeden op een longembolie?

Literatuur

Bernardi E, Camporese G, Büller HR, Siragusa S, Imberti D, Berchio A, Ghirarduzzi A, Verlato F, Anastasio R, Prati C, Piccioli A, Pesavento R, Bova C, Maltempi P, Zanatta N, Cogo A, Cappelli R, Bucherini E, Cuppini S, Noventa F, Prandoni P; Erasmus Study Group. Serial 2-point ultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: a randomized controlled trial. JAMA. 2008 Oct 8;300(14):1653-9. doi: 10.1001/jama.300.14.1653. PMID: 18840838.

Bhatt M, Braun C, Patel P, Patel P, Begum H, Wiercioch W, Varghese J, Wooldridge D, Alturkmani HJ, Thomas M, Baig M, Bahaj W, Khatib R, Kehar R, Ponnapureddy R, Sethi A, Mustafa A, Nieuwlaat R, Lim W, Bates SM, Lang E, Le Gal G, Righini M, Husainat NM, Kalot MA, Al Jabiri YN, Schünemann HJ, Mustafa RA. Diagnosis of deep vein thrombosis of the lower extremity: a systematic review and meta-analysis of test accuracy. Blood Adv. 2020 Apr 14;4(7):1250-1264. doi: 10.1182/bloodadvances.2019000960. PMID: 32227213; PMCID: PMC7160276.

Van Dam LF, Dronkers CEA, Gautam G, Eckerbom Å, Ghanima W, Gleditsch J, von Heijne A, Hofstee HMA, Hovens MMC, Huisman MV, Kolman S, Mairuhu ATA, Nijkeuter M, van de Ree MA, van Rooden CJ, Westerbeek RE, Westerink J, Westerlund E, Kroft LJM, Klok FA; Theia Study Group. Magnetic resonance imaging for diagnosis of recurrent ipsilateral deep vein thrombosis. Blood. 2020 Apr 16;135(16):1377-1385. Doi: 10.1182/blood.2019004114. PMID: 32016390.

van Dam LF, van den Hout WB, Gautam G, Dronkers CEA, Ghanima W, Gleditsch J, von Heijne A, Hofstee HMA, Hovens MMC, Huisman MV, Kolman S, Mairuhu ATA, Nijkeuter M, van de Ree MA, van Rooden CJ, Westerbeek RE, Westerink J, Westerlund E, Kroft LJM, Klok FA. Cost-effectiveness of magnetic resonance imaging for diagnosing recurrent ipsilateral deep vein thrombosis. Blood Adv. 2021 Mar 9;5(5):1369-1378. doi: 10.1182/bloodadvances.2020003849. PMID: 33661297; PMCID: PMC7948280.

Dronkers CEA, van der Hulle T, Le Gal G, Kyrle PA, Huisman MV, Cannegieter SC, Klok FA. Toward a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: Communication from the SSC of the ISTH. J Thromb Haemost. 2021 Jul;19(7):1834-1835. doi: 10.1111/jth.15357. PMID: 34176217.

Geersing, G. J., Zuithoff, N. P., Kearon, C., Anderson, D. R., Ten Cate-Hoek, A. J., Elf, J. L., Bates, S. M., Hoes, A. W., Kraaijenhagen, R. A., Oudega, R., Schutgens, R. E., Stevens, S. M., Woller, S. C., Wells, P. S., & Moons, K. G. (2014). Exclusion of deep vein thrombosis using the Wells rule in clinically important subgroups: individual patient data meta-analysis. BMJ (Clinical research ed.), 348, g1340. https://doi.org/10.1136/bmj.g1340

Geersing, G. J., Takada, T., Klok, F. A., Büller, H. R., Courtney, D. M., Freund, Y., Galipienzo, J., Le Gal, G., Ghanima, W., Kline, J. A., Huisman, M. V., Moons, K. G. M., Perrier, A., Parpia, S., Robert-Ebadi, H., Righini, M., Roy, P. M., van Smeden, M., Stals, M. A. M., Wells, P. S., … van Es, N. (2022). Ruling out pulmonary embolism across different healthcare settings: A systematic review and individual patient data meta-analysis. PLoS medicine, 19(1), e1003905. https://doi.org/10.1371/journal.pmed.1003905

de Jong CMM, van den Hout W, van Dijk CE, Heim N, van Dam LF, Dronkers C, Gautam G, Ghanima W, Gleditsch J, von Heijne A, Hofstee H, Hovens M, Huisman MV, Kolman S, Mairuhu ATA, van Mens TE, Nijkeuter M, van de Ree M, van Rooden JK, Westerbeek RE, Westerink J, Westerlund E, Kroft L, Klok FA. Cost-effectiveness of performing reference ultrasonography in patients with deep vein thrombosis. Thromb Haemost. 2023 Nov 20. doi: 10.1055/a-2213-9230. Epub ahead of print. PMID: 37984402.

Lensing AW, Prandoni P, Brandjes D, Huisman PM, Vigo M, Tomasella G, Krekt J, Wouter Ten Cate J, Huisman MV, Büller HR. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. N Engl J Med. 1989 Feb 9;320(6):342-5. doi: 10.1056/NEJM198902093200602. PMID: 2643771.

van der Pol LM, Bistervels IM, van Mens TE, van der Hulle T, Beenen LFM, den Exter PL, Kroft LJM, Mairuhu ATA, Middeldorp S, van Werkhoven JM, Ten Wolde M, Huisman MV, Klok FA. Lower prevalence of subsegmental pulmonary embolism after application of the YEARS diagnostic algorithm. Br J Haematol. 2018 Nov;183(4):629-635. doi: 10.1111/bjh.15556. Epub 2018 Sep 10. PMID: 30198551; PMCID: PMC6282699.

van der Pol LM, Tromeur C, Bistervels IM, Ni Ainle F, van Bemmel T, Bertoletti L, Couturaud F, van Dooren YPA, Elias A, Faber LM, Hofstee HMA, van der Hulle T, Kruip MJHA, Maignan M, Mairuhu ATA, Middeldorp S, Nijkeuter M, Roy PM, Sanchez O, Schmidt J, Ten Wolde M, Klok FA, Huisman MV; Artemis Study Investigators. Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism. N Engl J Med. 2019 Mar 21;380(12):1139-1149. doi: 10.1056/NEJMoa1813865. PMID: 30893534.

Parpia S, Takach Lapner S, Schutgens R, Elf J, Geersing GJ, Kearon C. Clinical pre-test probability adjusted versus age-adjusted D-dimer interpretation strategy for DVT diagnosis: A diagnostic individual patient data meta-analysis. J Thromb Haemost. 2020 Mar;18(3):669-675. doi: 10.1111/jth.14718. Epub 2020 Jan 14. PMID: 31869505.

Remy-Jardin M, Pistolesi M, Goodman LR, Gefter WB, Gottschalk A, Mayo JR, Sostman HD. Management of suspected acute pulmonary embolism in the era of CT angiography: a statement from the Fleischner Society. Radiology. 2007 Nov;245(2):315-29. doi: 10.1148/radiol.2452070397. Epub 2007 Sep 11. PMID: 17848685.

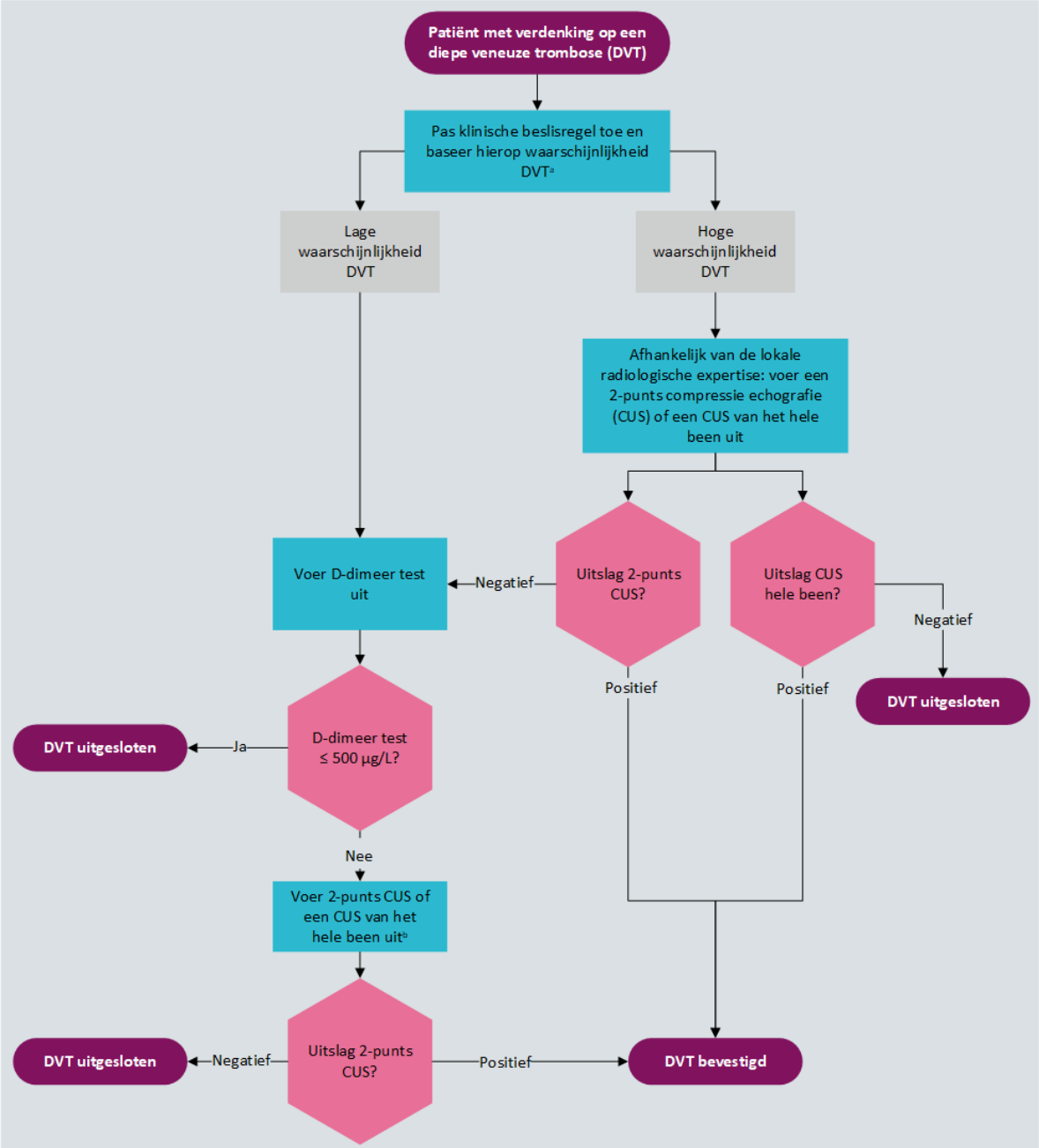
Stals, M. A. M., Takada, T., Kraaijpoel, N., van Es, N., Büller, H. R., Courtney, D. M., Freund, Y., Galipienzo, J., Le Gal, G., Ghanima, W., Huisman, M. V., Kline, J. A., Moons, K. G. M., Parpia, S., Perrier, A., Righini, M., Robert-Ebadi, H., Roy, P. M., van Smeden, M., Wells, P. S., … Klok, F. A. (2022). Safety and Efficiency of Diagnostic Strategies for Ruling Out Pulmonary Embolism in Clinically Relevant Patient Subgroups : A Systematic Review and Individual-Patient Data Meta-analysis. Annals of Internal medicine, 175(2), 244–255. https://doi.org/10.7326/M21-2625

Tan M, Mol GC, van Rooden CJ, Klok FA, Westerbeek RE, Iglesias Del Sol A, van de Ree MA, de Roos A, Huisman MV. Magnetic resonance direct thrombus imaging differentiates acute recurrent ipsilateral deep vein thrombosis from residual thrombosis. Blood. 2014 Jul 24;124(4):623-7. doi: 10.1182/blood-2014-04-566380. Epub 2014 Jun 13. PMID: 24928859.

Tan M, Velthuis SI, Westerbeek RE, VAN Rooden CJ, VAN DER Meer FJ, Huisman MV. High percentage of non-diagnostic compression ultrasonography results and the diagnosis of ipsilateral recurrent proximal deep vein thrombosis. J Thromb Haemost. 2010 Apr;8(4):848-50. doi: 10.1111/j.1538-7836.2010.03758.x. PMID: 20398187.

Bijlagen bij hoofdstuk diagnostiek bij vermoeden VTE

Stroomschema Diagnostiek bij vermoeden op een (recidief) DVT



DVT: Diepe veneuze trombose; CUS: Compressie Echografie.

Voetnoot
a. Indien echografie laagdrempelig beschikbaar is: Overweeg om de combinatie klinische beslisregel/D-dimeer test over te slaan en direct een 2-punts compressie-echografie te verrichten om een proximale DVT uit te sluiten of aan te tonen.
b. Bij patiënten met een hoge klinische waarschijnlijkheid van DVT in combinatie met een negatieve 2-punts CUS en D-dimeer test ≤ 500 µg/L, is het advies om de 2-punts CUS of de CUS van het hele been na 7 dagen te herhalen.

nederlandse internisten vereniging

Initiatiefnemende vereniging

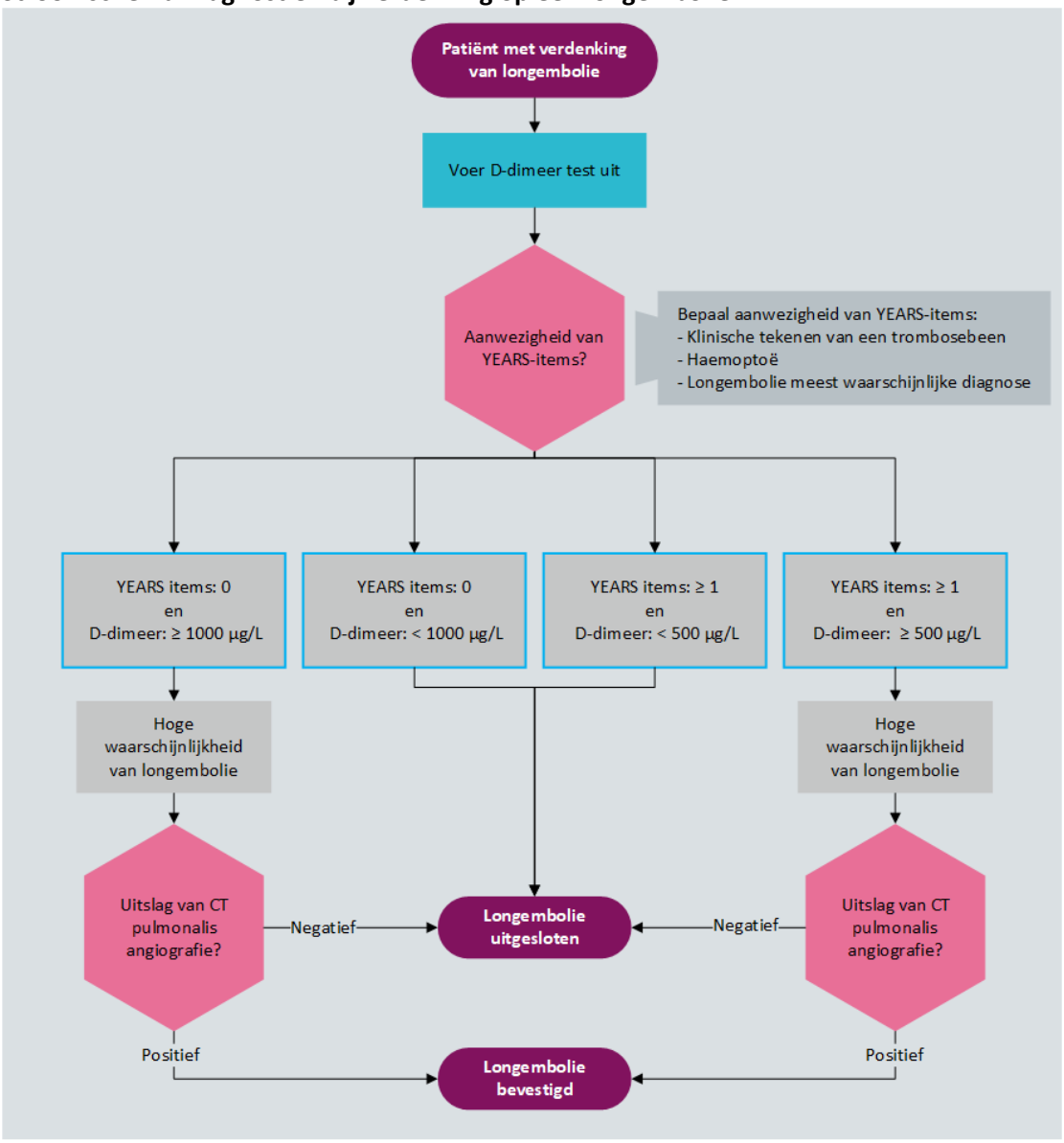
NB1: Dit stroomschema hoort bij de module 'Diagnostiek' van richtlijn 'Antitrombotisch beleid'. Lees altijd de overwegingen en aanbevelingen van de betreffende module voor nuances, eventuele afwijkende situaties en extra achtergrondinformatie.

NB2: Betrek de patiënt bij de besluitvorming.

Federatie Medisch Specialisten

Ontwikkeld door het Kennisinstituut van de Federatie Medisch Specialisten

Stroomschema Diagnostiek bij verdenking op een longembolie



nederlandse internisten vereniging

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NB2: Betrek de patiënt bij de besluitvorming.

Federatie Medisch Specialisten

Ontwikkeld door het Kennisinstituut van de Federatie Medisch Specialisten

Implementatieplan

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

15

(Sub)aanbeveling	**Sterkte van de aanbeveling**	**Bewijskracht per uitkomstmaat**	**Verkeerslicht per (sub)aanbeveling**
Aanbeveling 1 Pas een gevalideerde klinische beslisregel toe bij patiënten met een klinische verdenking van een DVT. Volg hierbij de stappen uit het stroomschema 'Diagnostiek bij vermoeden op een (recidief) DVT': 1. *Hoge waarschijnlijkheid DVT op basis van klinische beslisregel* Voer compressie-echografie uit om de aanwezigheid van een proximale DVT aan te tonen dan wel uit te sluiten. 2. *Lage waarschijnlijkheid DVT op basis van klinische beslisregel* Voer een D-dimeer test uit. - Indien D-dimeer test > 500 µg/L :Voer	**X** Sterk (doe/ gebruik) / □ Zwak (overweeg)	**Overall bewijskracht** □ **H** □ **M X L** □ **VL** □ **NG** **Range bewijskracht van alle uitkomstmaten** □ **H** □ **M X L** □ **VL** □ **NG** **OF** □ **voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in □ **ORANJE:** gebruik tabel B **X LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in

compressie-echografie uit om de aanwezigheid van een proximale DVT aan te tonen dan wel uit te sluiten. - Indien D-dimeer test ≤ 500 µg/L : proximale DVT is uitgesloten Indien echografie laagdrempelig beschikbaar is: Overweeg om de combinatie klinische beslisregel/D-dimeer test over te slaan en direct een 2-punts compressie-echografie te verrichten om een proximale DVT uit te sluiten of aan te tonen.			
Aanbeveling 2 Pas een gevalideerde klinische beslisregel toe bij patiënten met een klinische verdenking van een recidief DVT. Volg hierbij de stappen uit het stroomschema 'Diagnostiek bij vermoeden op een (recidief) DVT': 1. *Hoge waarschijnlijkheid DVT op basis van klinische beslisregel* Voer compressie-echografie uit om de aanwezigheid van een proximale DVT aan te tonen dan wel uit te sluiten. Er is sprake van een recidief proximale DVT in het geval van een abnormale 2-punts compressie-echografie in een nieuw veneus	**X** Sterk (doe/ gebruik) / □ Zwak (overweeg)	**Overall bewijskracht** □ **H** □ **M** **X L** □ **VL** □ **NG** **Range bewijskracht van alle uitkomstmaten** □ **H** □ **M** **X L** □ **VL** □ **NG** **OF** □ **voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in □ **ORANJE:** gebruik tabel B **X LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in

segment of indien het niet comprimeerbare oude veneuze segment met ≥ 4 mm is toegenomen. 2. *Lage waarschijnlijkheid DVT op basis van klinische beslisregel* Voer een D-dimeer test uit. - Indien D-dimeer test > 500 µg/L : Voer compressie-echografie uit om de aanwezigheid van een proximale DVT aan te tonen dan wel uit te sluiten. Er is sprake van een recidief proximale DVT in het geval van een abnormale 2-punts compressie-echografie in een nieuw veneus segment of indien het oude niet comprimeerbare veneuze segment met ≥ 4 mm is toegenomen. - Indien D-dimeer test ≤ 500 µg/L : proximale DVT uitgesloten Indien de compressie echografie niet eenduidig is: overweeg om een MRDTI toe te passen teneinde een recidief DVT aan te tonen dan wel uit te sluiten. Indien echografie laagdrempelig			

beschikbaar is: Overweeg om de combinatie klinische beslisregel/D-dimeer test over te slaan en direct een 2-punts compressie-echografie te verrichten om een recidief proximale DVT uit te sluiten,- of aan te tonen.			
Sluit een eerste of herhaalde episode van longembolie uit met behulp van een lage klinische voorafkans (vastgesteld met een gevalideerde beslisregel) en een normale D-dimeer test bij patiënten met een verdenking op een longembolie. Overweeg hierbij om het YEARS-algoritme te gebruiken. Sluit een eerste of herhaalde episode van een longembolie uit of toon een longembolie aan met een CTPA bij patiënten met een hoge klinische waarschijnlijkheid of afwijkende D-dimeer test. Volg hierbij de stappen uit het stroomschema 'Diagnostiek bij verdenking op een longembolie'.	**X** Sterk (doe/ gebruik) / □ Zwak (overweeg)	**Overall bewijskracht** □ **H** □ **M** **X L** □ **VL** □ **NG** **Range bewijskracht van alle uitkomstmaten** □ **H** **X M** **X L** □ **VL** □ **NG** **OF** □ **voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in □ **ORANJE:** gebruik tabel B **X LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in

Implementatietabel

Tabel A: (De-)Implementatietabel met impuls analyse

Aanbevelingen – eerste DVT, recidief DVT en PE			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**□ Ongewenste praktijkvariatie** **X Nieuwe evidentie** **□ Anders** **Toelichting:** De laatste versie van de module dateerde uit 2008. Daarom is besloten een nieuwe module te maken op grond van de recentste inzichten en studies.		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**□ < 1000** **□ < 5000** **X 5000-40.000** **□ > 40.000**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	**□ Ja**: hoe verhoudt deze aanbeveling zich tot de andere aanbevelingen uit deze module/ richtlijn of uit andere richtlijnen(modules)? Dient hier rekening mee gehouden te worden bij de implementatie of kan dit worden gezien als een losstaande aanbeveling? **Toelichting:** [toelichting] **X Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	Verschil in aanbevelingen tussen deze module en de NHG-Standaard	Adviezen van deze module zijn in lijn met de huidige ACCP en ASH richtlijnen t.a.v. de diagnostiek van

		Diepe veneuze trombose en longembolie	patienten met een verdenking van DVT of (recidief) PE
b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	Onvoldoende kennis onder zorgverleners over deze module	Aansluiting van de module bij de internationale richtlijnen
c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*		
d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	Verschillende meningen/inzichten tussen medische disciplines waaronder huisartsen en specialisten (internisten en longartsen)	
e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*		Het volgen van de diagnostische stroomdiagrammen vraagt geen andere organisatie van de huidige processen in de ziekenhuizen, zoals meer capaciteit et cetera
f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*		De kosten van de diagnostische stroomdiagrammen zijn lager dan als deze stroomdiagrammen niet worden toegepast

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	□ Patiënt/ cliënt (naaste) **X** Professional **X** Beroepsvereniging □ Ziekenhuis(bestuurder) □ Zorgverzekeraars/ NZa □ Zorginstituut [duiding nodig]
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	Aanbevelingen verwerken in lokale ziekenhuisprotocollen, deze zo nodig herzien en deze implementeren op de werkvloer in de klinische praktijk. Daarnaast communicatie vanuit de beroepsverenigingen (met name NIV en NVALT) richting hun achterban.
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X** < 1 jaar □ < 2 jaar □ < 3 jaar *[toelichting]*
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	□ **Ja* X Nee** **Toelichting:** geen bijzondere aandacht in de vorm van plaatsing op de implementatie agenda, maar wel communicatie vanuit de beroepsverenigingen NIV en NVALT richting hun achterban.

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

Evidence tabellen

Evidence table for systematic reviews of diagnostic test accuracy studies

Research question:
Subquestion-1: What is the diagnostic value of clinical decision rules in patients with suspected first episode or relapsed deep vein thrombosis (DVT)?
Subquestion-2: What is the diagnostic value of clinical decision rules in patients with suspected first episode or relapsed pulmonary embolism (PE)?

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
Geersing, 2022 Study characteristics and results for individual studies are extracted from the SR Geersing, 2022 (unless stated otherwise)	SR and Individual-Patient Data (IPD) meta-analysis *Literature search from 1 January 1995 until 1 November 2021* **A:** Sanson, 2000 B: Wicki, 2001 C: Perrier, 2004 D: Ghanima, 2005 E: Perrier, 2005 F: van Belle, 2006 G: Goekoop, 2007 H: Righini, 2008 I: Douma, 2011	Inclusion criteria SR: patients with clinically suspected PE, at least 1 of the clinical decision rules (CDRs) of interest assessed and as a reference standard: imaging or clinical follow-up for those not receiving anticoagulant treatment. Exclusion criteria SR: More than 80% missing data for variables necessary for imputation (5 studies excluded for >80% missing D-dimer data) *23 studies were included in the IPDA meta-analysis with 14 studies in the referred secondary care setting (A-N).* Important patient characteristics: N: **Total** 35 248; **Included** 17 052 PE, n (%): 1864 (19%); 20% Care setting: Mix; Referred secondary care	IPD meta-analysis: Several diagnostic strategies were compared. Clinical decision rules included the Wells score, revised Geneva score, and the YEARS algorithm. The D-dimer threshold was either fixed (500 µg/L), age-adjusted (age x 10 µg/L in patients aged >50 years) or dependent on pretest probability (PPT) for Wells and Geneva. For the PTP adjusted D-dimer levels low probability (Wells score of ≤4 or Geneva score of ≤5) has a D-dimer cut-off of 1000 ng/ml and	Imaging or clinical follow-up in those in whom PE was ruled out without imaging and who thus did not receive anticoagulant treatment. Prevalence (%) [based on refence test at specified cut-off point] **A:** 30.9 B: 27.2 C: 23.7 D: 22.0 E: 26.1 F: 21.2 G: 12.6 H: 21.3 I: 23.8 J: 26.3 K: 40.9 L: 19.2	All studies had 3 months follow-up periods.	Negative predictive value (NPV) can be post hoc estimated from the two outcomes measures reported by the authors: • Diagnostic failure rate: "the predicted 3-month VTE incidence after exclusion of PE without imaging at baseline." (= false negatives) • Efficiency: "the proportion of individuals classified by the strategy as PE considered excluded without imaging tests" (True negatives plus false negatives)	Study quality (ROB): QUADAS-2 was used to report risk of bias per individual study. Most studies had low risk of bias and applicability concerns, with most common being an unclear risk of bias for the reference standard (four studies: B, C, E, G). C and E were the only two studies with high risk of patient selection and index test. M also had unclear risk of bias in the index test. For the index test there is also unclear (study M) or high (studies C and E) applicability concerns. Finally risk of bias in flow and timing was high for studies C and D and unclear for study M. Place of the index test in the clinical pathway: replacement of scan.

	J: Galipienzo, 2012 K: Mos, 2014 L: Righini, 2014 M: Penaloza, 2017 N: van der Hulle T, 2017 O: Kline, 2002 P: Kearon, 2006 Q: Kline, 2006 R: Runyon, 2007 S: Geersing, 2012 T: Kline, 2012 U: Kline, 2008 V: Schouten, 2014 W: Kearon, 2019 <u>Study design</u>: IPD meta-analysis of studies with a prospective follow-up or cross-sectional design <u>Setting and Country</u>: Different countries and settings <u>Source of funding and conflicts of interest:</u>	**A** 517 517 (30.9%) Referred secondary care and inpatients **B** 1089 1089 (27.2%) Referred secondary care **C** 965 965 (23.7%) Referred secondary care **D** 432 432 (22.0%) Referred secondary care **E** 755 755 (26.1%) Referred secondary care **F** 3296 3296 (21.2%) Referred secondary care and inpatients **G** 876 876 (12.6%) Referred secondary care **H** 1692 1692 (21.3%) Referred secondary care **I** 807 807 (23.8%) Referred secondary care and inpatients **J** 240 240 (26.3%) Referred secondary care **K** 279 279 (40.9%) Referred secondary care and inpatients **L** 3324 3324 (19.2%) Referred secondary care **M** 705 705 (21.7%) Referred secondary care **N** 3448 3448 (13.7%) Referred secondary care and inpatients **O** 948 948 (19.6%) Self-referral emergency care **P** 1123 1123 (15.0%) Primary healthcare and inpatients **Q** 2255 2255 (4.8%) Self-referral emergency care	moderate probability (score of ≥6) has a D-dimer cut-off of 500 ng/ml. In the YEARS algorithm the D-dimer threshold is dependent on clinical pretest probability (CPTP) assessment (with a higher D-dimer threshold for patients with a low CPTP).	M: 21.7 N: 13.7 O: 19.6 P: 15.0 Q: 4.8 R: 3.3 S: 12.2 T: 17.0 U: 7.1 V: 39.8 W: 7.4 <u>Complete data:</u> Unclear from the information provided in the study for how many participants complete outcome data was available. Authors include % missing data per variable. This indicates no missing data for VTE diagnosis at baseline or follow-up except for study E (Schouten, 2014) with 0.3% missing values. No reason was given for the missing values. In case of missing values in the diagnostic strategies and outcomes, imputation was used. Multilevel chained equations included all items in		Point estimates as well as 95% prediction intervals (CI) were given. NPV point estimates and 95% CI were calculated with: as following: NPV = 1 -failure rate. **Clinical decision rule** / **Failure rate** / **Efficiency** / **NPV** Wells + any D-dimer: 0.75 (95%CI 0.50 to 1.13) / 29.57 (95%CI 25.39 to 34.12) / 98.6 Wells + D-dimer <500 µg/L: 0.32 (95%CI 0.17 to 0.60) / 27.77 (95%CI 23.05 to 33.03) / 98.6 Wells + age-adjusted D-dimer: 0.65 (95%CI 0.43 to 0.99) / 32.91 (95%CI 27.85 to 38.39) / 97.6 Wells + PTP D-dimer: 3.06 (95%CI 2.47 to 3.78) / 48.78 (95%CI 43.64 to 53.94) / 97.6 Geneva + any D-dimer: 1.17 (95%CI 0.79 to 1.74) / 30.46 (95%CI 26.75 to 34.44) / 98.1 Geneva + D-dimer <500 µg/L: 0.37 (95%CI 0.19 to 0.74) / 28.77 (95%CI 26.20 to 31.48) / 98.1	<u>Choice of cut-off point</u>: Important to reliably exclude individuals for further diagnostic testing with (expensive) scans while identifying all relevant patients. Thus, interested in a high number of true negatives and a low number of false negatives. The 500 µg/L threshold has less false negatives but results in more scans. The age-adjusted D-dimer threshold and YEARS algorithm set higher D-dimer threshold depending on age or clinical information to avoid unnecessary testing. The authors conclude that all strategies have acceptable safety (low predicted failure rates). Efficiency was higher for adapted D-dimer thresholds. To avoid exclusion of entire studies, 1-stage multilevel chained equations were used to impute missing values. Multilevel chained equations included all items in the diagnostic strategies and the outcome. Ten imputation data sets were created, and the analysis results were combined using the Rubin rule. Subgroup analyses were done by sex, age, cancer, and previous venous thromboembolism (VTE).

	The study was funded by personal Vidi grant from the Dutch Research Council. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. One author received grants from several pharmaceutical companies, the Dutch thrombosis association, The Netherlands Organisation for Health Research and Development and the Dutch Heart foundation. One author has participated in advisory boards from several pharmaceutical companies, receive lecture honoraria and grants from several	**R** 1187 1187 (3.3%) Self-referral emergency care **S** 597 597 (12.2%) Primary healthcare **T** 678 678 (17.0%) Self-referral emergency care and inpatients **U** 7889 7889 (7.1%) Self-referral emergency care **V** 129 129 (39.8%) Primary healthcare and nursing homes **W** 2017 2017 (7.4%) Primary healthcare and inpatients		the diagnostic strategies and the outcome. Ten imputation data sets were created, and the analysis results were combined using the Rubin rule.		<table><tr><td>Geneva + age-adjusted D-dimer</td><td>0.81 (95%CI 0.51 to 1.27)</td><td>35.25 (95%CI 32.76 to 37.82)</td><td>97.0</td></tr><tr><td>Geneva + PTP D-dimer</td><td>2.95 (95%CI 2.34 to 3.71)</td><td>43.02 (95%CI 38.28 to 47.31)</td><td>97.0</td></tr><tr><td>YEARS</td><td>2.10 (95%CI 1.59 to 2.75)</td><td>43.38 (95%CI 38.86 to 48.01)</td><td>95.6</td></tr></table> Sensitivity and specificity <table><tr><th>Clinical decision rule</th><th>Sensitivity</th><th>Specificity</th></tr><tr><td>Wells + any D-dimer</td><td>98.38 (95%CI 95.87 to 99.41)</td><td>36.89 (95%CI 32.53 to 41.47)</td></tr><tr><td>Wells + D-dimer <500 µg/L</td><td>99.59 (95%CI 99.10 to 99.82)</td><td>35.21 (95%CI 30.19 to 40.57)</td></tr><tr><td>Wells + age-adjusted D-dimer</td><td>98.93 (95%CI 98.15 to 99.39)</td><td>41.58 (95%CI 36.42 to 46.93)</td></tr><tr><td>Wells + PTP D-dimer</td><td>93.25 (95%CI 91.91 to 94.38)</td><td>60.80 (95%CI 56.24 to 65.19)</td></tr></table>	Heterogeneity: In general, patient characteristics and reference specification were similar. There is heterogeneity in the availability and definition of items included in the diagnostic strategies. Most studies used Wells rules or collected these variables based on Geneva scoring items. Various D-dimer assays were used, but with the same threshold >500 ng/mL. A sensitivity analysis was performed including only studies with data on all diagnostic strategies. This resulted in similar failure rate and efficiency estimates (see table below). <table><tr><th>Clinical decision rule</th><th>Failure rate</th><th>Efficiency</th></tr><tr><td>Wells + D-dimer <500 µg/L</td><td>0.32 (95%CI 0.09 to 0.91)</td><td>23.72 (95%CI 20.17 to 27.68)</td></tr><tr><td>Wells + age-adjusted D-dimer</td><td>0.50 (95%CI 0.27 to 0.92)</td><td>28.86 (95%CI 24.82 to 33.26)</td></tr><tr><td>Wells + PTP D-dimer</td><td>3.02 (95%CI 2.32 to 3.92)</td><td>45.83 (95%CI 41.27 to 50.46)</td></tr></table>

	pharmaceutical companies.					Geneva + any D-dimer	97.75 (95%CI 93.86 to 99.27)	39.25 (95%CI 34.57 to 44.14)
						Geneva + D-dimer <500 µg/L	99.53 (95%CI 98.88 to 99.80)	37.23 (95%CI 34.00 to 40.57)
						Geneva + age-adjusted D-dimer	98.51 (95%CI 97.37 to 99.16)	45.27 (95%CI 42.63 to 47.95)
						Geneva + PTP D-dimer	98.51 (95%CI 97.37 to 99.16)	45.27 (95%CI 42.63 to 47.95)
						YEARS	94.18 (95%CI 92.70 to 95.38)	54.49 (95%CI 50.82 to 58.12)
						Geneva + D-dimer <500 µg/L	0.40 (95%CI 0.19 to 0.83)	28.73 (95%CI 25.63 to 32.05)
						Geneva + age-adjusted D-dimer	0.72 (95%CI 0.43 to 1.21)	35.23 (95%CI 32.26 to 38.32)
						Geneva + PTP D-dimer	2.88 (95%CI 2.22 to 3.74)	43.05 (95%CI 37.94 to 48.32)
						YEARS	2.02 (95%CI 1.42 to 2.85)	40.33 (95%CI 36.94 to 43.82)
Stals, 2022 Study characteristics and results for individual studies are extracted from the SR Stals, 2022 (unless stated	SR and Individual-Patient Data (IPD) meta-analysis *Literature search from 1 January 1995 until 1 January 2021* **A**: Kline, 2012 **B**: Douma, 2011 **C**: Goekoop, 2007	Inclusion criteria SR: patients with clinically suspected PE, at least 1 of the clinical decision rules (CDRs) of interest assessed and as a reference standard: imaging or clinical follow-up for those not receiving anticoagulant treatment. Exclusion criteria SR: only qualitative D-dimer measurements performed and patients with only low clinical pretest probability. *16 studies included* Important patient characteristics:	IPD meta-analysis: Several diagnostic strategies were compared. Clinical decision rules included the Wells score, revised Geneva score, and the YEARS algorithm. The D-dimer threshold was either fixed (500 µg/L) or age-adjusted (age x 10 µg/L in patients aged >50 years) for Wells and Geneva. In	Imaging or clinical follow-up in those in whom PE was ruled out without imaging and who thus did not receive anticoagulant treatment. Reference test and cut-off point(s): A: CTPA or 30 days clinical follow-up B: CTPA or 3 months clinical follow-up	Only A (Kline 2012) had a follow-up of 30 days, all other studies had 3 months follow-up periods.	Not enough information was provided to report on sensitivity or specificity. Negative predictive value (NPV) can be post hoc estimated from the two outcomes measures reported by the authors: • Diagnostic failure rate: "the predicted 3-month VTE incidence after exclusion of PE without		Study quality (ROB): QUADAS-2 was used to report risk of bias per individual study. Most studies had low risk of bias and applicability concerns, with most common being an unclear risk of bias for the reference standard (five studies: C, E, I, J, L). J and K were the only two studies with high risk of patient selection and index test. A and P also had unclear risk of bias in the index test. For the index test there is also unclear (study P) or high (studies J and K)

otherwise)	**D**: Righini, 2014 **E**: Schouten, 2014 **F**: van Belle, 2006 **G**: Van der Hulle, 2017 **H**: Mos, 2014 **I**: Wicki, 2001 **J**: Perrier, 2004 **K**: Perrier, 2005 **L**: Righini, 2008 **M**: Kearon, 2019 **N**: Galipienzo, 2012 **O**: Ghanima, 2005 **P**: Penaloza, 2017 <u>Study design</u>: IPD meta-analysis of studies with a prospective follow-up or cross-sectional design <u>Setting and Country</u>: Different countries, but in hospital patients (mostly outpatients, but some inpatients included)		N	Median Age (IQR), yrs	Female, n (%)	Inpatients, n (%)	Previous VTE, n (%)	Tachycardia, n (%)	the YEARS algorithm the D-dimer threshold is dependent on clinical pretest probability (CPTP) assessment (with a higher D-dimer threshold for patients with a low CPTP). <u>Per study:</u> A: Wells score and revised Geneva score with D-dimer threshold 1000 µg/L for "PE unlikely" patients B: Wells rule and revised Geneva score (both original and simplified version) with D-dimer testing (threshold, 500 µg/L). All four CDRs negative for PE to be unlikely. C: Dichotomized Wells score combined with D-dimer testing (threshold, 500 µg/L) "D: Wells or revised Geneva score combined with D-dimer testing (threshold of 500 µg/L in patients aged <50 y and age-adjusted threshold in	C: CTPA or V/Q or 3 months clinical follow-up D: CTPA or 3 months clinical follow-up E: CTPA or V/Q or 3 months clinical follow-up F: CTPA or 3 months clinical follow-up G: CTPA or 3 months clinical follow-up H: CTPA or 3 months clinical follow-up I: Lung scan J: CTPA or 3 months clinical follow-up K: Multidetector row CT and CUS or 3 months clinical follow-up L: CTPA or 3 months clinical follow-up M: CTPA or 3 months clinical follow-up N: CTPA or 3 months clinical follow-up O: MSCTor 3 months clinical follow-up P: CTPA or V/Q or 3 months clinical follow-up Prevalence (%) [based on refence test at specified cut-off point] **A:** 23 B: 24 C: 13 D: 19 E: 28		imaging at baseline." (= false negatives) • Efficiency: "the proportion of individuals classified by the strategy as PE considered excluded without imaging tests" (True negatives plus false negatives) Point estimates as well as 95% prediction intervals (CI) were given. NPV point estimates and 95% CI were calculated as following: NPV = 1 -failure rate. Wells plus fixed D-dimer NPV point estimate = (26-0.36)/26 = 0.986 NPV 95% CI = 0.981-0.987 Wells plus age-adjusted D-dimer NPV point estimate = (32-0.76)/32 = 0.976 NPV 95% CI = 0.969 - 0.978 YEARS NPV point estimate = (41-1.8)/41= 0.956 NPV 95% CI = 0.934-0.965	applicability concerns. Finally risk of bias in flow and timing was high for studies O and J and unclear for study M. <u>Place of the index test in the clinical pathway</u>: replacement of scan. <u>Choice of cut-off point</u>: Important to reliably exclude individuals for further diagnostic testing with (expensive) scans while identifying all relevant patients. Thus, interested in a high number of true negatives and a low number of false negatives. The 500 µg/L threshold has less false negatives but results in more scans. The age-adjusted D-dimer threshold and YEARS algorithm set higher D-dimer threshold depending on age or clinical information to avoid unnecessary testing. The authors conclude that all strategies have acceptable safety (low predicted failure rates). Efficiency was higher for adapted D-dimer thresholds. To avoid exclusion of entire studies, 1-stage multilevel chained equations were used to impute missing values (including systematically missing values). Multilevel chained equations included all items in the diagnostic strategies and the outcome.
		Overall	20 553	58 (43–71)	12 161 (59)	1606 (7.8)	2941 (14)	4383 (21)			
		A	334	57 (47–66)	200 (60)	334 (100)	50 (15)	60 (18)			
		B	807	54 (40–67)	487 (60)	163 (20)	39 (4.8)	184 (23)			
		C	876	50 (38–65)	549 (63)	0 (0)	84 (9.6)	166 (19)			
		D	3324	63 (53–73)	1887 (57)	0 (0)	466 (14)	722 (22)			
		E	294	76 (67–84)	195 (66)	0 (0)	52 (18)	64 (22)			
		F	3296	52 (39–68)	1897 (58)	605 (18)	427 (13)	690 (21)			
		G	3448	54 (40–67)	2142 (62)	468 (14)	360 (10)	693 (20)			
		H	279	54 (42–68)	164 (59)	36 (13)	279 (100)	59 (21)			
		I	1089	62 (46–76)	597 (55)	0 (0)	202 (19)	236 (22)			
		J	965	63 (45–77)	562 (58)	0 (0)	167 (17)	186 (19)			
		K	1692	61 (45–75)	923 (55)	0 (0)	300 (18)	369 (22)			

	Source of funding and conflicts of interest: The study was funded by the Dutch Research Council. The sponsor was not involved in the study and the authors had final responsibility for study design, oversight, data verification, analyses and accuracy and completeness of the manuscript. Two authors disclosed receiving personal fees for consulting and payment or honoraria for educational events such as presentations from Sobi, Pfizer, UCB, Argenx, Amgen, Sanofi, Bayer, Novartis in the 36 months preceding publication of the study.	**L**	63 755(45–76)	453 (60)	0 (0)	142 (19)	176 (23)	patients aged ≥50 y) " E: Wells score with D-dimer testing (set-up with qualitative assay, but quantitative data was collected in 50% of the participants) F: Dichotomized Wells score combined with D-dimer testing (threshold, 500 µg/L) G: YEARS score with D-dimer (threshold, 1000 µg/L if 0 YEARS items and 500 µg/L if 1–3 YEARS items) H: Dichotomized Wells score combined with D-dimer testing (threshold, 500 µg/L) I: Geneva score with D-dimer testing J: Geneva score with D-dimer testing (threshold, 500 µg/L) K: Geneva score with D-dimer testing (threshold, 500 µg/L) L: Geneva score with D-dimer testing (threshold, 500 µg/L) M: Wells score with D-dimer testing (threshold, 1000 µg/L for low clinical probability and 500 µg/L for moderate clinical probability)	F: 21 G: 14 H: 41 I: 27 J: 24 K: 21 L: 26 M: 7,4 N: 26 O: 22 P: 22 Complete data: Unclear from the information provided in the study for how many participants complete outcome data was available. Authors include % missing data per variable. This indicates no missing data for VTE diagnosis at baseline or follow-up except for study E (Schouten, 2014) with 0.3% missing values. No reason was given for the missing values. In case of missing values in the diagnostic strategies and outcomes, imputation was used. Multilevel chained equations included all items in			Ten imputation data sets were created, and the analysis results were combined using the Rubin rule. Subgroup analyses were done by sex, age, cancer, and previous venous thromboembolism (VTE). VTE detected during follow-up could be a new event and thus unrelated to the index presentation. The authors performed a sensitivity analysis in which only VTE events diagnosed at baseline with imaging was used as the outcome. This sensitivity analysis resulted in slightly lower point estimates for failure rate. Heterogeneity: In general, patient characteristics and reference specification were similar. There is heterogeneity in the availability and definition of items included in the diagnostic strategies. Most studies used Wells rules or collected these variables based on Geneva scoring items. Various D-dimer assays were used and D-dimer threshold can vary between studies, most used >500 µg/L. For the IPD meta-analysis raw D-dimer assay data was used to calculate estimates based on the D-dimer thresholds specified by the authors. The
		M	53 2017(38–66)	1335 (66)	1 (0)	164 (8.1)	398 (20)				
		N	67 240(54–78)	122 (51)	0 (0)	38 (16)	56 (23)				
		O	58 432(43–73)	231 (54)	0 (0)	44 (10)	79 (18)				
		P	61 705(46–76)	419 (59)	0 (0)	127 (18)	246 (35)				

			N: Dichotomized Wells score combined with D-dimer testing (threshold, 500 µg/L) O: Algorithm based on the Hyers criteria combined with D-dimer testing (threshold, 400 µg/L) P: Pulmonary embolism rule-out criteria (PERC) with D-dimer testing	the diagnostic strategies and the outcome. Ten imputation data sets were created, and the analysis results were combined using the Rubin rule.			authors made forest plots and gave I2 statistics for the subgroup analyses. Based on these forest plots there was considerable between study heterogeneity for both failure rate and efficiency of each diagnostic strategy. With wider confidence intervals for patients with cancer and patients with a history of VTE.
Geersing, 2014 Study characteristics and results for individual studies are extracted from the SR Geersing, 2014 (unless stated otherwise)	IPD meta-analysis *Literature search from 2006 to supplement studies from previous meta-analysis* A: Anderson 2000 B: Kraaijenhagen 2002 C: Schutgens 2003 D: Wells 2003 E: Elf 2009 F: Kearon 2001 G: Anderson 2003 H: Bates 2003 I: Stevens 2004 J: Kearon 2005 K: Oudega 2005 L: Toll 2006	<u>Inclusion criteria SR</u>: consecutive outpatients with suspected DVT; have the results of any D-dimer testing before reference testing; data on all predictors that form the Wells rule; categorised patients with the Wells rule before venous imaging (reference test); document the presence or absence of proximal DVT by an acceptable reference test. <u>Exclusion criteria SR</u>: None mentioned (besides the inclusion criteria). For the current guideline only studies in the secondary/hospital patients were included. *13 studies were included in the IPDA meta-analysis with 10 studies in the hospital outpatient setting (A-J).* <u>Important patient characteristics</u>: Of the 10 002 patients in the IPD meta-analysis, 1864 (19%) had proximal DVT. The median age was 59 years and 62% of patients were female.	A low score on the Wells rule (≤1) combined with a negative D-dimer test (quantitative or qualitative). For quantitative D-dimer assays the cut-off as reported in the original study was used (most studies <500 µg/L). For qualitative D-dimer (point of care) assays, only a positive or negative test result was reported.	Reference tests were either compression ultrasonography (CUS) or venography at initial presentation, or, if venous imaging was not performed, an uneventful follow-up for at least three months. Reference test and cut-off point(s): A: CUS or venography at baseline or 3 months uneventful follow-up B: CUS at baseline or 3 months uneventful follow-up C: CUS at baseline or 3 months uneventful follow-up D: CUS at baseline or 3 months uneventful follow-up	All studies had a minimal follow-up of three months.	Not enough information was provided to report on sensitivity or specificity. Negative predictive value (NPV) can be post hoc estimated from the two outcomes measures reported by the authors: • Diagnostic failure rate: the predicted 3-month DVT incidence after exclusion of DVT without imaging at baseline. (= false negatives) • Efficiency: the proportion of individuals classified DVT excluded based on scoring ≤1 on the Wells rule and a negative D-dimer test (=True	<u>Study quality (ROB):</u> The authors provide limited information about study quality. Many of the included studies did not explicitly blind of the outcome (DVT) assessor to the results of the Wells rule and D-dimer testing. This can lead to an overoptimistic estimate of the value of the Wells rule and D-dimer testing for assessing DVT. <u>Place of the index test in the clinical pathway</u>: replacement of scan. <u>Choice of cut-off point</u>: Important to reliably exclude individuals for further diagnostic testing with (expensive) scans. Thus, interested in a high number of true negatives and low number of false positives. <u>Heterogeneity</u>: There was considerable heterogeneity

	M: AMUSE study 2009 Study design: IPD meta-analysis of studies with a prospective follow-up design Setting and Country: 13 studies in Canada, the Netherlands, the United States, and Sweden. Outpatients in the primary and hospital setting (with subgroup analysis for care setting) Source of funding and conflicts of interest: The study received no funding. The authors declare: "no support from any organisation for the submitted work; no financial relationships	<table><tr><th></th><th>N</th><th>DVT, n (%)</th><th>Care setting</th><th>D-dimer</th><th>Inclusion</th></tr><tr><td>Total Included</td><td>10 002 4511</td><td>1864 (19%) unknown</td><td>Mix Hospital</td><td>Mix yes</td><td>no Yes</td></tr><tr><td>A</td><td>153</td><td>26 (17)</td><td>Hospital</td><td>yes</td><td>yes</td></tr><tr><td>B</td><td>1756</td><td>411 (23)</td><td>Hospital</td><td>yes</td><td>yes</td></tr><tr><td>C</td><td>814</td><td>318 (39)</td><td>Hospital</td><td>yes</td><td>yes</td></tr><tr><td>D</td><td>541</td><td>121 (22)</td><td>Hospital</td><td>yes</td><td>yes</td></tr><tr><td>E</td><td>325</td><td>52 (16)</td><td>Hospital</td><td>yes</td><td>yes</td></tr><tr><td>F</td><td>429</td><td>61 (14)</td><td>Hospital</td><td>no</td><td>no</td></tr><tr><td>G</td><td>1075</td><td>190 (18)</td><td>Hospital</td><td>no</td><td>no</td></tr><tr><td>H</td><td>550</td><td>55 (10)</td><td>Hospital</td><td>no</td><td>no</td></tr><tr><td>I</td><td>436</td><td>42 (10)</td><td>Hospital</td><td>no</td><td>no</td></tr><tr><td>J</td><td>809</td><td>42 (5)</td><td>Hospital</td><td>no</td><td>no</td></tr><tr><td>K</td><td>1295</td><td>289 (22)</td><td>Primary</td><td>yes</td><td>no</td></tr><tr><td>L</td><td>791</td><td>126 (16)</td><td>Primary</td><td>yes</td><td>no</td></tr><tr><td>M</td><td>1028</td><td>131 (13)</td><td>Primary</td><td>yes</td><td>no</td></tr></table>		E: CUS or venography at baseline or 3 months uneventful follow-up Prevalence (%) [based on refence test at specified cut-off point] A: 17 B: 23 C: 39 D: 22 E: 16 For how many participants were no complete outcome data available? In all studies complete outcome data was available, except for study **B** (Kraaijenhagen 2002) with 3% missing values for DVT. No reason was given for the missing values. In case of missing values in the diagnostic tests (D-dimer and any predictors included in the Wells rule), reference tests or DVT outcome, imputation with multivariable regression was used.		negatives plus false negatives) Point estimates as well as 95% prediction intervals (CI) were given. NPV point estimates and 95% CI were calculated as following: NPV = 1 -failure rate. Wells ≤1 plus negative D-dimer Failure rate: 0.9% (95%CI 0.0 to 1.9) Efficiency: 23.1% (95%CI 12.8 to 38.3) NPV: 96.1% (95%CI 95 to 100%)	between the studies in prevalence estimates. This likely contributed to the relatively wide prediction intervals calculated by the authors. The main analyses were repeated with prevalence set at 15% (a prevalence that best reflects a European or primary care based healthcare setting). But this was not done for the secondary analysis for care setting that was reported in in this guideline, so it is unclear how the heterogeneity in prevalence between studies affected the results.

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<td>with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.”</td>
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<td>Imputation was done per dataset, therefore studies without data on D-dimer testing were not included in the results. It is unclear how many imputation data sets were created.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parpia, 2019

Study characteristics and results for individual studies are extracted from the SR Geersing, 2024 (unless stated otherwise)</td>
<td>IPD meta-analysis

Literature search from 1 January 1995 until 1 January 2021

C: Schutgens 2003
L: Toll 2006
E: Elf 2009
N: Linkins 2013

<u>Study design</u>: prospective follow-up

<u>Setting and Country</u>: 4 studies; one in Canada, two in the Netherlands, and one in Sweden. Outpatient</td>
<td><u>Inclusion criteria SR</u>: consecutive outpatients with suspected DVT; have the results of a quantitative D-dimer test before reference testing; data on all predictors that form the Wells rule; categorised patients with the Wells rule before venous imaging (reference test); document the presence or absence of proximal DVT by an acceptable reference test.

<u>Exclusion criteria SR</u>: Patients with a high clinical pre-test probability (CPTP) based on the Wells score were excluded as D-dimer is not recommended to exclude DVT in these patients. 814 of 3368 patients were excluded for this reason.

4 studies were included.

<u>Important patient characteristics</u>:
Of the 3368 patients in the four studies, 814. 2254 patients with low or moderate CPTP were included in the analysis. A DVT diagnosis was present in 12% of all patients, prevalence varied from 5% to 31% between studies. 64% of all patients</td>
<td>A low score on the Wells rule (≤1) combined with a negative D-dimer test (quantitative or qualitative).
For quantitative D-dimer assays the cut-off as reported in the original study was used (most studies <500 µg/L). For qualitative D-dimer (point of care) assays, only a positive or negative test result was reported.</td>
<td>Reference tests were either compression ultrasonography (CUS) or venography at initial presentation, or, if venous imaging was not performed, an uneventful follow-up for at least three months.

Reference test and cut-off point(s):
A: CUS or venography at baseline or 3 months uneventful follow-up
B: CUS at baseline or 3 months uneventful follow-up
C: CUS at baseline or 3 months uneventful follow-up
D: CUS at baseline or 3 months uneventful follow-up</td>
<td>All studies had a minimal follow-up of three months.</td>
<td>Table gives point estimates (95% CI).
<table>
<tr><th>D-dimer</th><th>Efficiency</th><th>NPV</th><th>Sensitivity</th><th>Specicity</th></tr>
<tr><td><500 µg/L</td><td>38.9 (29.1-48.7)</td><td>99.8 (99.5-100)</td><td>99.0 (97.8-100.0)</td><td>45.2 (39.6 50.9)</td></tr>
<tr><td>age x 10 µg/L for >50 years</td><td>47.4 (35.3-59.3)</td><td>99.7 (99.4-100.0)</td><td>98.0 (96.3-99.5)</td><td>54.7 (48.3-61.2)</td></tr>
</table></td>
<td><u>Study quality (ROB):</u>The authors provide limited information about quality of the included studies.

<u>Place of the index test in the clinical pathway</u>: replacement of scan.

<u>Choice of cut-off point</u>:
Important to reliably exclude individuals for further diagnostic testing with (expensive) scans. Thus, interested in a high number of true negatives and low number of false positives.

Heterogeneity: studies differed in prevalence of DVT and distribution of patients in Wells 0 or 1-2. Having a smaller proportion of patients in the 0 Wells group reduces specificity and the amount of patients testing negative.
In addition, different D-dimer assays (three latex</td>
</tr>
</table>

	setting with three studies in hospital and one in primary care. <u>Source of funding and conflicts of interest:</u> The study was funded by Hamilton Health Sciences New Investigator Fund. Dr Kearon is supported by the Jack Hirsh Professorship in Thromboembolism. Dr Geersing is supported by a Veni and Vidi from the Dutch Research Council (NWO/ZonMw). All authors declared no conflicts of interest.	were female, the mean age was 59 years and 44% had low CPTP. **C** 517 / 162 (31) / 58 (17) / 332 (64) / 28 (5) / 24 (5) / 5 (1) / 111 (21) / 47 (9) / 284 (55) / 181 (35) / 37 (7) / 196 (38) / 195 (38) / 322 (62) / D-dimer assay: Tinaquant **L** 443 / 48 (11) / 59 (17) / 278 (63) / 14 (3) / 21 (5) / 31 (7) / 97 (22) / 109 (25) / 277 (62) / 193 (44) / 50 (11) / 232 (52) / 95 (21) / 348 (79) / VIDAS/ Tinaquant **E** 274 / 25 (9) / 58 (17) / 169 (62) / 4 (1) / 5 (2) / 8 (3) / 51 (19) / 17 (6) / 125 (46) / 59 (22) / 25 (9) / 114 (42) / 151 (55) / 123 (45) / Auto dimer **N** 1320 / 61 (5) / 60 (16) / 848 (64) / 62 (5) / 94 (7) / 34 (3) / 137 (10) / 84 (6) / 580 (44) / 293 (22) / 50 (4) / 547 (41) / 693 (53) / 627 (48) / Triage **Total** 2554 / 296 (12) / 59 (17) / 1627 (64) / 108 (4) / 144 (6) / 78 (3) / 396 (16) / 257 (10) / 1266 (50) / 726 (28) / 162 (6) / 1089 (43) / 1134 (44) / 1420 (56)		E: CUS or venography at baseline or 3 months uneventful follow-up Prevalence (%) [based on refence test at specified cut-off point] C: 31 L: 11 E: 25 N: 61 For how many participants were no complete outcome data available? Unclear. Authors mention few patients were lost to follow-up, but do not provide a numerical indication nor any reasons for loss to follow-up.			agglutination assays and one enzyme-linked immunosorbent assays [ELISA]) were used in different settings (three studies in secondary setting, one study in primary care setting).

		Country	Netherlands	Netherlands	Sweden	Canada	–		
		Care setting	Secondary	Primary	Secondary	Secondary	–		

SR= systematic review; IPD = Individual-Patient Data; CDR = clinical decision rule; CT = computed tomography; CTPA = computed tomography pulmonary angiography; CUS = compression ultrasonography; MSCT = multislice spiral computed tomography; NA = not available; PE = pulmonary embolism; PERC = pulmonary embolism rule-out criteria; V/Q = ventilation–perfusion scan, US= ultrasonography.

Table of quality assessment for systematic reviews of diagnostic studies

Research question:

Subquestion-1: What is the diagnostic value of clinical decision rules in patients with suspected first episode or relapsed deep vein thrombosis (DVT)?

Subquestion-2: What is the diagnostic value of clinical decision rules in patients with suspected first episode or relapsed pulmonary embolism (PE)?

Study **First author, year**	**Appropriate and clearly focused question?** **Yes/no/unclear**	**Comprehensive and systematic literature search?** **Yes/no/unclear**	**Description of included and excluded studies?** **Yes/no/unclear**	**Description of relevant characteristics of included studies?** **Yes/no/unclear**	**Assessment of scientific quality of included studies?** **Yes/no/unclear**	**Enough similarities between studies to make combining them reasonable?** **Yes/no/unclear**	**Potential risk of publication bias taken into account?** **Yes/no/unclear**	**Potential conflicts of interest reported?** **Yes/no/unclear**
Geersing, 2022	Yes, "to assess the capability of ruling out PE by available diagnostic strategies across all possible settings."	Yes, "MEDLINE was first searched from January 1, 1995 to August 25, 2016 (this was recently updated until November 1, 2021)". Full description available as appendix in the protocol registration.	Yes, potentially relevant studies that are excluded at final selection (after reading the full text) are referenced in text with reasons.	Unclear, characteristics related to PICO such as patient population, type of clinical decision rule and D-dimer test, reference and timing/setting are described. Although type of clinical decision rule was only described overall, not available for each individual study.	Yes, authors assessed studies using the QUADAS-2, reported risk of bias with +/?/- and took this into account in the evidence synthesis. They do not specify the reasons for lower ratings in individual studies. Therefore, it is not possible to	Yes	No, the potential risk of publication bias is not discussed.	No, source of funding SR is clear but not for individual studies.

Study First author, year	Appropriate and clearly focused question? Yes/no/unclear	Comprehensive and systematic literature search? Yes/no/unclear	Description of included and excluded studies? Yes/no/unclear	Description of relevant characteristics of included studies? Yes/no/unclear	Assessment of scientific quality of included studies? Yes/no/unclear	Enough similarities between studies to make combining them reasonable? Yes/no/unclear	Potential risk of publication bias taken into account? Yes/no/unclear	Potential conflicts of interest reported? Yes/no/unclear
					reproduce their QUADAS-2 rating per study.			
Stals, 2022	Yes, "To evaluate the safety and efficiency of the Wells and revised Geneva scores combined with fixed and adapted D-dimer thresholds, as well as the YEARS algorithm, for ruling out acute pulmonary embolism (PE) in relevant patient subgroups defined by sex, age, cancer, and previous venous thromboembolism (VTE)"	Yes, "MEDLINE was searched from 1 January 1995 until 1 January 2021 to retrieve studies that had evaluated diagnostic strategies for PE". Full description available as appendix.	Yes, potentially relevant studies that are excluded at final selection (after reading the full text) are referenced in text with reasons.	Yes, characteristics related to PICO such as patient population, type of clinical decision rule and D-dimer test, reference and timing/setting are described.	Unclear, authors assessed studies using the QUADAS-2 and reported risk of bias with +/?/-, but do not take this into account in the evidence synthesis. They do not specify the reasons for lower ratings in individual studies. Therefore, it is not possible to reproduce their QUADAS-2 rating per study.	Yes	No, the potential risk of publication bias is not discussed.	No, source of funding SR is clear but not for individual studies.
Geersing, 2014	Yes, "To assess the accuracy of the Wells rule for excluding deep vein thrombosis and whether this accuracy applies to different subgroups of patients."	Unclear, authors updated the search from a previous meta-analysis by searching for additional papers after 2006 with a validated algorithm for finding diagnostic studies. Full description search algorithm available as	Yes, potentially relevant studies that are excluded at final selection (after reading the full text) are specified in the supplement.	Yes, description characteristics related to PICO such as patient population, application Wells rule and D-dimer test, reference and timing/setting.	No, authors discuss methodological considerations in the discussion but did not use a quality scoring tool or checklist.	Unclear, there was considerable heterogeneity in study prevalence (ranging 5-39%) for the main analysis (including both primary and secondary care settings). A	No, the potential risk of publication bias is not discussed.	No, source of funding SR is clear but not for individual studies.

Study First author, year	Appropriate and clearly focused question? Yes/no/unclear	Comprehensive and systematic literature search? Yes/no/unclear	Description of included and excluded studies? Yes/no/unclear	Description of relevant characteristics of included studies? Yes/no/unclear	Assessment of scientific quality of included studies? Yes/no/unclear	Enough similarities between studies to make combining them reasonable? Yes/no/unclear	Potential risk of publication bias taken into account? Yes/no/unclear	Potential conflicts of interest reported? Yes/no/unclear
		supplement. However, unclear which databases were searched.				sensitivity analysis was done for the main analysis to assess the influence of prevalence. However, in the current guideline results from a secondary analysis are used for the hospital setting only (prevalence ranging 16-39%).		

Risk of bias assessment diagnostic accuracy studies (QUADAS II, 2011)

Research question:
Subquestion-1: What is the diagnostic value of clinical decision rules in patients with suspected first episode or relapsed deep vein thrombosis (DVT)?
Subquestion-2: What is the diagnostic value of clinical decision rules in patients with suspected first episode or relapsed pulmonary embolism (PE)?

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
Geersing, 2022	Was a consecutive or random sample of patients enrolled? Yes, only prospective follow-up or cross-sectional studies were included in the individual patient level meta-analysis. Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Yes	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear, the reference test was always done after the index test and likely part of the patient record.	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes, part of the reference standard was clinical follow-up but not all patients underwent imaging procedures. Did patients receive the same reference standard? No Were all patients included in the analysis? Yes, authors used multiple imputation for missing values but do not report whether there were follow-up issues in the original study.	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: UNCLEAR**	CONCLUSION Could the patient flow have introduced bias? **RISK: UNCLEAR**	

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
Stals, 2022	Was a consecutive or random sample of patients enrolled? Yes, only prospective follow-up or cross-sectional studies were included in the individual patient level meta-analysis. Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Yes	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear, the reference test was always done after the index test and likely part of the patient record. Nine studies adjudicated outcomes and three studies adjudicated deaths, but four studies did not adjudicate outcomes.	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes, part of the reference standard was clinical follow-up but not all patients underwent imaging procedures. Did patients receive the same reference standard? No Were all patients included in the analysis? Yes, authors used multiple imputation for missing values but do not report whether there were follow-up issues in the original study.	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: UNCLEAR**	CONCLUSION Could the patient flow have introduced bias? **RISK: UNCLEAR**	
Geersing, 2014	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition? Yes, although CUS is less able to identify recurrent events, notably ipsilateral ones.	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
	Yes	Yes, but for D-dimer testing both a qualitative and quantitative assay was used. With a mix of thresholds for the quantitative assays (the threshold used within the study)	Were the reference standard results interpreted without knowledge of the results of the index test? No, in some studies DVT assessors were not blinded.	Did patients receive the same reference standard? No part of the reference standard was clinical follow-up but not all patients underwent imaging procedures. Were all patients included in the analysis? Yes, authors used multiple imputation for missing values but do not report whether there were follow-up issues in the original study.	Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: HIGH**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: HIGH**	CONCLUSION Could the patient flow have introduced bias? **RISK: UNCLEAR**	
Parpia, 2019	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? No, excluded patients with Wells score >2 which can result in higher NPV (critical outcome).	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Yes	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No, in some studies DVT assessors were not blinded.	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? No part of the reference standard was clinical follow-up but not all patients underwent imaging procedures. Were all patients included in the analysis?	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
				Unclear, authors do not report whether there were follow-up issues and did not use imputation.	
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: HIGH**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: HIGH**	CONCLUSION Could the patient flow have introduced bias? **RISK: UNCLEAR**	

Table of excluded studies

Reference	Reason for exclusion
van der Hulle, T., van Es, N., den Exter, P. L., van Es, J., Mos, I. C. M., Douma, R. A., Kruip, M. J. H. A., Hovens, M. M. C., Ten Wolde, M., Nijkeuter, M., Ten Cate, H., Kamphuisen, P. W., Büller, H. R., Huisman, M. V., & Klok, F. A. (2017). Is a normal computed tomography pulmonary angiography safe to rule out acute pulmonary embolism in patients with a likely clinical probability? A patient-level meta-analysis. Thrombosis and haemostasis, 117(8), 1622–1629. https://doi.org/10.1160/TH17-02-0076	Older patient-level meta-analysis than Geersing 2022 and Stals 2022
Kearon, C., de Wit, K., Parpia, S., Schulman, S., Afilalo, M., Hirsch, A., Spencer, F. A., Sharma, S., D'Aragon, F., Deshaies, J. F., Le Gal, G., Lazo-Langner, A., Wu, C., Rudd-Scott, L., Bates, S. M., Julian, J. A., & PEGeD Study Investigators (2019). Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability. The New England journal of medicine, 381(22), 2125–2134. https://doi.org/10.1056/NEJMoa1909159	Study included in Geersing 2022 and Stals 2022
Mos, I. C., Douma, R. A., Erkens, P. M., Kruip, M. J., Hovens, M. M., van Houten, A. A., Hofstee, H. M., Kooiman, J., Klok, F. A., Büller, H. R., Kamphuisen, P. W., Huisman, M. V., & Prometheus Study Group (2014). Diagnostic outcome management study in patients with clinically suspected recurrent acute pulmonary embolism with a structured algorithm. Thrombosis research, 133(6), 1039–1044. https://doi.org/10.1016/j.thromres.2014.03.050	Study included in Geersing 2022 and Stals 2022
van der Hulle, T., Cheung, W. Y., Kooij, S., Beenen, L. F. M., van Bemmel, T., van Es, J., Faber, L. M., Hazelaar, G. M., Heringhaus, C., Hofstee, H., Hovens, M. M. C., Kaasjager, K. A. H., van Klink, R. C. J., Kruip, M. J. H. A., Loeffen, R. F., Mairuhu, A. T. A., Middeldorp, S., Nijkeuter, M., van der Pol, L. M., Schol-Gelok, S., … YEARS study group (2017). Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet (London, England), 390(10091), 289–297. https://doi.org/10.1016/S0140-6736(17)30885-1	Study included in Geersing 2022 and Stals 2022
Fabiá Valls, M. J., van der Hulle, T., den Exter, P. L., Mos, I. C., Huisman, M. V., & Klok, F. A. (2015). Performance of a diagnostic algorithm based on a prediction rule, D-dimer and CT-scan for pulmonary embolism in patients with previous venous thromboembolism. A systematic review and meta-analysis. Thrombosis and haemostasis, 113(2), 406–413. https://doi.org/10.1160/TH14-06-0488	Older systematic review than Geersing 2022 and Stals 2022
Bhatt, M., Braun, C., Patel, P., Patel, P., Begum, H., Wiercioch, W., Varghese, J., Wooldridge, D., Alturkmani, H. J., Thomas, M., Baig, M., Bahaj, W., Khatib, R., Kehar, R., Ponnapureddy, R., Sethi, A., Mustafa, A., Nieuwlaat, R., Lim, W., Bates, S. M., … Mustafa, R. A. (2020). Diagnosis of deep vein thrombosis of the lower extremity: a systematic review and meta-analysis of test accuracy. Blood advances, 4(7), 1250–1264. https://doi.org/10.1182/bloodadvances.2019000960	wrong I&C (reports on relevant outcomes for d-dimer standalone without incorporating clinical decision rules)
van der Pol, L. M., Tromeur, C., Bistervels, I. M., Ni Ainle, F., van Bemmel, T., Bertoletti, L., Couturaud, F., van Dooren, Y. P. A., Elias, A., Faber, L. M., Hofstee, H. M. A., van der Hulle, T., Kruip, M. J. H. A., Maignan, M., Mairuhu, A. T. A., Middeldorp, S., Nijkeuter, M., Roy, P. M., Sanchez, O., Schmidt, J., … Artemis Study Investigators (2019). Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism. The New England journal of medicine, 380(12), 1139–1149. https://doi.org/10.1056/NEJMoa1813865	Wrong population (pregnant women)
Righini, M., Van Es, J., Den Exter, P. L., Roy, P. M., Verschuren, F., Ghuysen, A., Rutschmann, O. T., Sanchez, O., Jaffrelot, M., Trinh-Duc, A., Le Gall, C., Moustafa, F., Principe, A., Van Houten, A. A., Ten Wolde, M., Douma, R. A.,	Study included in Geersing 2022 and Stals 2022

Hazelaar, G., Erkens, P. M., Van Kralingen, K. W., Grootenboers, M. J., … Le Gal, G. (2014). Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA, 311(11), 1117–1124. https://doi.org/10.1001/jama.2014.2135	
Righini, M., Robert-Ebadi, H., Elias, A., Sanchez, O., Le Moigne, E., Schmidt, J., Le Gall, C., Cornuz, J., Aujesky, D., Roy, P. M., Chauleur, C., Rutschmann, O. T., Poletti, P. A., Le Gal, G., & CT-PE-Pregnancy Group (2018). Diagnosis of Pulmonary Embolism During Pregnancy: A Multicenter Prospective Management Outcome Study. Annals of internal medicine, 169(11), 766–773. https://doi.org/10.7326/M18-1670	Wrong population (pregnant women)
Lim, W., Le Gal, G., Bates, S. M., Righini, M., Haramati, L. B., Lang, E., Kline, J. A., Chasteen, S., Snyder, M., Patel, P., Bhatt, M., Patel, P., Braun, C., Begum, H., Wiercioch, W., Schünemann, H. J., & Mustafa, R. A. (2018). American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. Blood advances, 2(22), 3226–3256. https://doi.org/10.1182/bloodadvances.2018024828	Wrong design (no information to calculate outcome measures)
Geersing, G. J., Erkens, P. M., Lucassen, W. A., Büller, H. R., Cate, H. T., Hoes, A. W., Moons, K. G., Prins, M. H., Oudega, R., van Weert, H. C., & Stoffers, H. E. (2012). Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: prospective cohort study. BMJ (Clinical research ed.), 345, e6564. https://doi.org/10.1136/bmj.e6564	Wrong setting (primary care)
Gibson, N. S., Schellong, S. M., Kheir, D. Y., Beyer-Westendorf, J., Gallus, A. S., McRae, S., Schutgens, R. E., Piovella, F., Gerdes, V. E., & Buller, H. R. (2009). Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. Journal of thrombosis and haemostasis : JTH, 7(12), 2035–2041. https://doi.org/10.1111/j.1538-7836.2009.03635.x	Wrong design (set up to compare different ultrasound strategies, thus different references)
Kleinjan, A., Di Nisio, M., Beyer-Westendorf, J., Camporese, G., Cosmi, B., Ghirarduzzi, A., Kamphuisen, P. W., Otten, H. M., Porreca, E., Aggarwal, A., Brodmann, M., Guglielmi, M. D., Iotti, M., Kaasjager, K., Kamvissi, V., Lerede, T., Marschang, P., Meijer, K., Palareti, G., Rickles, F. R., … Büller, H. R. (2014). Safety and feasibility of a diagnostic algorithm combining clinical probability, d-dimer testing, and ultrasonography for suspected upper extremity deep venous thrombosis: a prospective management study. Annals of internal medicine, 160(7), 451–457. https://doi.org/10.7326/M13-2056	Wrong design (set up to compare different ultrasound strategies, thus different references)
Takada, T., van Doorn, S., Parpia, S., de Wit, K., Anderson, D. R., Stevens, S. M., Woller, S. C., Ten Cate-Hoek, A. J., Elf, J. L., Kraaijenhagen, R. A., Schutgens, R. E. G., Wells, P. S., Kearon, C., Moons, K. G. M., & Geersing, G. J. (2020). Diagnosing deep vein thrombosis in cancer patients with suspected symptoms: An individual participant data meta-analysis. Journal of thrombosis and haemostasis : JTH, 18(9), 2245–2252. https://doi.org/10.1111/jth.14900	Wrong design (set-up to explore reasons for reduced diagnostic accuracy in cancer patients suspected of DVT); All underlying studies included in IPD analyses Geersing 2014
van Es, N., van der Hulle, T., van Es, J., den Exter, P. L., Douma, R. A., Goekoop, R. J., Mos, I. C., Galipienzo, J., Kamphuisen, P. W., Huisman, M. V., Klok, F. A., Büller, H. R., & Bossuyt, P. M. (2016). Wells Rule and d-Dimer Testing to Rule Out Pulmonary Embolism: A Systematic Review and Individual-Patient Data Meta-analysis. Annals of internal medicine, 165(4), 253–261. https://doi.org/10.7326/M16-0031	Older systematic review and IPD meta-analysis than Geersing 2022 and Stals 2022
Revel, M. P., Sanchez, O., Couchon, S., Planquette, B., Hernigou, A., Niarra, R., Meyer, G., & Chatellier, G. (2012). Diagnostic accuracy of magnetic	Wrong comparator (only patients

resonance imaging for an acute pulmonary embolism: results of the 'IRM-EP' study. Journal of thrombosis and haemostasis : JTH, 10(5), 743–750. https://doi.org/10.1111/j.1538-7836.2012.04652.x	positive outcome on clinical probability and D-dimer testing); wrong design (set up to evaluate usage MRI in diagnosing pulmonary embolism)
Elf, J. L., Strandberg, K., Nilsson, C., & Svensson, P. J. (2009). Clinical probability assessment and D-dimer determination in patients with suspected deep vein thrombosis, a prospective multicenter management study. Thrombosis research, 123(4), 612–616. https://doi.org/10.1016/j.thromres.2008.04.007	Included in IPD analyses Geersing 2014 and Parpia 2020
Engelberger, R. P., Aujesky, D., Calanca, L., Staeger, P., Hugli, O., & Mazzolai, L. (2011). Comparison of the diagnostic performance of the original and modified Wells score in inpatients and outpatients with suspected deep vein thrombosis. Thrombosis research, 127(6), 535–539. https://doi.org/10.1016/j.thromres.2011.02.008	Wrong design (compare original and modified Wells score, not enough information to calculate diagnostic accuracy information for Wells score + d-dimer)
Hendriksen, J. M., Lucassen, W. A., Erkens, P. M., Stoffers, H. E., van Weert, H. C., Büller, H. R., Hoes, A. W., Moons, K. G., & Geersing, G. J. (2016). Ruling Out Pulmonary Embolism in Primary Care: Comparison of the Diagnostic Performance of "Gestalt" and the Wells Rule. Annals of family medicine, 14(3), 227–234. https://doi.org/10.1370/afm.1930	Wrong setting (primary care)
Di Nisio, M., Van Sluis, G. L., Bossuyt, P. M., Büller, H. R., Porreca, E., & Rutjes, A. W. (2010). Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. Journal of thrombosis and haemostasis : JTH, 8(4), 684–692. https://doi.org/10.1111/j.1538-7836.2010.03771.x	Wrong design (comparing different diagnostic test, no information combination clinical decision rules + d-dimer)
Huisman, M. V., & Klok, F. A. (2013). Diagnostic management of acute deep vein thrombosis and pulmonary embolism. Journal of thrombosis and haemostasis : JTH, 11(3), 412–422. https://doi.org/10.1111/jth.12124	Wrong publication (narrative review)
Lucassen, W. A., Douma, R. A., Toll, D. B., Büller, H. R., & van Weert, H. C. (2010). Excluding pulmonary embolism in primary care using the Wells-rule in combination with a point-of care D-dimer test: a scenario analysis. BMC family practice, 11, 64. https://doi.org/10.1186/1471-2296-11-64	Wrong setting (primary care)
Linkins, L. A., Bates, S. M., Lang, E., Kahn, S. R., Douketis, J. D., Julian, J., Parpia, S., Gross, P., Weitz, J. I., Spencer, F. A., Lee, A. Y., O'Donnell, M. J., Crowther, M. A., Chan, H. H., Lim, W., Schulman, S., Ginsberg, J. S., & Kearon, C. (2013). Selective D-dimer testing for diagnosis of a first suspected episode of deep venous thrombosis: a randomized trial. Annals of internal medicine, 158(2), 93–100. https://doi.org/10.7326/0003-4819-158-2-201301150-00003	Included in Parpia 2019
Robert-Ebadi, H., Mostaguir, K., Hovens, M. M., Kare, M., Verschuren, F., Girard, P., Huisman, M. V., Moustafa, F., Kamphuisen, P. W., Buller, H. R., Righini, M., & Le Gal, G. (2017). Assessing clinical probability of pulmonary embolism: prospective validation of the simplified Geneva score. Journal of thrombosis and haemostasis : JTH, 15(9), 1764–1769. https://doi.org/10.1111/jth.13770	Subgroup analysis in same cohort as Righini 2014

de Wit, K., Al-Haimus, F., Hu, Y., Ikesaka, R., Chan, N., Ibrahim, Q., Klyn, J., Clayton, N., & Germini, F. (2022). Comparison of YEARS and Adjust-Unlikely D-dimer Testing for Pulmonary Embolism in the Emergency Department. Annals of emergency medicine, S0196-0644(22)01118-0. Advance online publication. https://doi.org/10.1016/j.annemergmed.2022.09.014	Wrong reference (30 days instead of 3 months follow up for pulmonary embolism diagnosis)
Riva, N., Camporese, G., Iotti, M., Bucherini, E., Righini, M., Kamphuisen, P. W., Verhamme, P., Douketis, J. D., Tonello, C., Prandoni, P., Ageno, W., & PALLADIO Study Investigators (2018). Age-adjusted D-dimer to rule out deep vein thrombosis: findings from the PALLADIO algorithm. Journal of thrombosis and haemostasis : JTH, 16(2), 271–278. https://doi.org/10.1111/jth.13905	Wrong design (set up to compare different ultrasound strategies after D-dimer testing, thus different references)

Zoekverantwoording

Algemene informatie

Richtlijn: NIV antitrombotisch beleid	
Uitgangsvraag: UV1, UV2 Wat is de optimale diagnostiek van patiënten met een vermoeden op een VTE?	
Database(s): Ovid/Medline, Embase	Datum: 15-12-2022
Periode: 2009-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	

5 ***Zoekopbrengst***

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	57	30	64*
RCTs	20	11	24*
Observationele studies	381	131	420*
Overig	268	68	273
Totaal			508*

****in Rayyan***

Zoekstrategie

Embase

No.	Query	Results
#28	#9 AND #27 sleutelartikelen gevonden in SR,RCT, OBS	3
#27	#21 OR #22 OR #23	458
#26	#15 NOT #23 NOT #22 NOT #21 Overige diagnostische studies	268
#25	#23 NOT #22 NOT #21 OBS	381
#24	#22 NOT #21 RCT	20
#23	#15 AND (#19 OR #20)	420
#22	#15 AND #18	31
#21	#15 AND #17 SR	57
#20	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de	13681486

	OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#19	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6767914
#18	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1839814

#17	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#16	#9 AND #15	3
#15	#11 AND #12	725
#14	#9 NOT #13	2
#13	#9 AND #11	3
#12	'sensitivity and specificity'/de OR sensitiv*:ab,ti OR specific*:ab,ti OR predict*:ab,ti OR 'roc curve':ab,ti OR 'receiver operator':ab,ti OR 'receiver operators':ab,ti OR likelihood:ab,ti OR 'diagnostic error'/exp OR 'diagnostic accuracy'/exp OR 'diagnostic test accuracy study'/exp OR 'inter observer':ab,ti OR 'intra observer':ab,ti OR interobserver:ab,ti OR intraobserver:ab,ti OR validity:ab,ti OR kappa:ab,ti OR reliability:ab,ti OR reproducibility:ab,ti OR ((test NEAR/2 're-test'):ab,ti) OR ((test NEAR/2 'retest'):ab,ti) OR 'reproducibility'/exp OR accuracy:ab,ti OR 'differential diagnosis'/exp OR 'validation study'/de OR 'measurement precision'/exp OR 'diagnostic value'/exp OR 'reliability'/exp OR 'predictive value'/exp OR ppv:ti,ab,kw OR npv:ti,ab,kw	9522259
#11	#10 AND [1-1-2009]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	1448
#10	#5 NOT (('adolescent'/exp OR 'child'/exp OR adolescent*:ti,ab,kw OR child*:ti,ab,kw OR schoolchild*:ti,ab,kw OR infant*:ti,ab,kw OR girl*:ti,ab,kw OR boy*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenager*:ti,ab,kw OR youth*:ti,ab,kw OR pediatr*:ti,ab,kw OR paediatr*:ti,ab,kw OR puber*:ti,ab,kw) NOT ('adult'/exp OR 'aged'/exp OR 'middle aged'/exp OR adult*:ti,ab,kw OR man:ti,ab,kw OR men:ti,ab,kw OR woman:ti,ab,kw OR women:ti,ab,kw))	2771
#9	#6 OR #7 OR #8	5
#8	'diagnosis of pulmonary embolism with d-dimer adjusted to clinical probability' NOT guy NOT winger	1

#7	'pregnancy-adapted years algorithm for diagnosis of suspected pulmonary embolism'	2
#6	'simplified diagnostic management of suspected pulmonary embolism (the years study): a prospective, multicentre, cohort study'	2
#5	#2 AND #3 AND #4	2832
#4	'd dimer'/exp OR 'd dimer':ti,ab,kw OR 'crosslinked fibrin degradation product':ti,ab,kw OR 'fibrin degradation product d dimer':ti,ab,kw	41232
#3	'clinical decision rule'/exp OR 'decision making'/exp OR 'diagnostic test'/exp OR ((decision* NEAR/3 (making OR rule*)):ti,ab,kw) OR 'clinical pretest probabilit*':ti,ab,kw OR 'c ptp':ti,ab,kw	1770358
#2	'venous thromboembolism'/exp OR 'deep vein thrombosis'/exp OR 'lung embolism'/exp OR (((venous OR vein OR lung OR pulmonary) NEAR/3 (embol* OR microembol* OR thromboembol*)):ti,ab,kw) OR vte:ti,ab,kw OR dvt:ti,ab,kw OR ((deep NEAR/3 (thromb* OR 'blood clot*' OR embol*)):ti,ab,kw)	234618
#1	'2022 esc guidelines on cardio-oncology developed in collaboration with the european hematology association (eha), the european society for therapeutic radiology and oncology'	2

Ovid/Medline

#	Searches	Results
19	9 not 16 not 15 not 14 overige diagnostische studies	68
18	16 not 15 not 14 OBS	131
17	15 not 14 RCT	11
16	9 and (12 or 13)	156
15	9 and 11	19
14	9 and 10 SR	30
13	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6	5309800

	(pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	
12	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4314474
11	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1569546
10	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	635722
9	7 and 8	240

8	exp "Sensitivity and Specificity"/ or (Sensitiv* or Specific*).ti,ab. or (predict* or ROC-curve or receiver-operator*).ti,ab. or (likelihood or LR*).ti,ab. or exp Diagnostic Errors/ or (inter-observer or intra-observer or interobserver or intraobserver or validity or kappa or reliability).ti,ab. or reproducibility.ti,ab. or (test adj2 (re-test or retest)).ti,ab. or "Reproducibility of Results"/ or accuracy.ti,ab. or Diagnosis, Differential/ or Validation Study/	7633306
7	6 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	323
6	limit 5 to yr="2009 -Current"	345
5	4 not ((Adolescent/ or Child/ or Infant/ or adolescen*.ti,ab,kf. or child*.ti,ab,kf. or schoolchild*.ti,ab,kf. or infant*.ti,ab,kf. or girl*.ti,ab,kf. or boy*.ti,ab,kf. or teen.ti,ab,kf. or teens.ti,ab,kf. or teenager*.ti,ab,kf. or youth*.ti,ab,kf. or pediatr*.ti,ab,kf. or paediatr*.ti,ab,kf. or puber*.ti,ab,kf.) not (Adult/ or adult*.ti,ab,kf. or man.ti,ab,kf. or men.ti,ab,kf. or woman.ti,ab,kf. or women.ti,ab,kf.))	433
4	1 and 2 and 3	436
3	Fibrin Fibrinogen Degradation Products/ or d dimer.ti,ab,kf. or crosslinked fibrin degradation product.ti,ab,kf. or fibrin degradation product d dimer.ti,ab,kf.	19200
2	Clinical Decision Rules/ or Decision Support Techniques/ or Decision Making/ or Diagnostic Tests, Routine/ or (decision* adj3 (making or rule*)).ti,ab,kf. or 'clinical pretest probabilit*'.ti,ab,kf. or 'c ptp'.ti,ab,kf.	291438
1	Venous Thromboembolism/ or exp Venous Thrombosis/ or exp Pulmonary Embolism/ or ((venous or vein or lung or pulmonary) adj3 (embol* or microembol* or thromboembol*)).ti,ab,kf. or vte.ti,ab,kf. or dvt.ti,ab,kf. or (deep adj3 (thromb* or 'blood clot*' or embol*)).ti,ab,kf.	146483

Module 2 Follow-up VTE

Autorisatie en geldigheid

Autorisatiedatum:	*pending*
Eerstvolgende beoordeling actualiteit	volgende cyclus binnen het cluster Antitrombotisch beleid
Geautoriseerd door:	*pending*
Belangrijkste wijzigingen t.o.v. vorige versie:	n.v.t., het betreft een nieuwe module
Herbevestiging:	n.v.t.
Regiehouder:	Nederlandse Internisten Vereniging

Uitgangsvraag

Hoe dienen patiënten met een VTE opgevolgd te worden?

Inleiding

Bij de nazorg voor patiënten met een veneuze trombo-embolie gaat de meest aandacht uit naar voorkomen van recidief ziekte en bloedingen, en is er een belangrijke focus op de beslissing om na 3 maanden de antistolling te stoppen of te continueren. Recidief ziekte en bloedingen zijn inderdaad geassocieerd met mortaliteit en morbiditeit, en leiden tot een afname van de kwaliteit van leven. Er zijn echter nog meer ziekte-gerelateerde complicaties die een stempel drukken op het herstel van de patiënt en de mogelijkheid het leven weer op te pakken na de diagnose. Tot de helft van de patiënten met veneuze trombo-embolie blijkt maanden na de diagnose en adequate antistollingsbehandeling nog restklachten te hebben die functioneel herstel belemmeren. Dit wordt het post-trombotisch syndroom en post-longembolie syndroom genoemd. Aangezien functioneel herstel een belangrijke zo niet de belangrijkste uitkomst van behandeling van veneuze trombo-embolie is vanuit het perspectief van de patiënt, zou het nazorg traject ingericht moeten zijn op het detecteren en behandelen van alle relevante complicaties. Studies naar een optimale nazorg van longembolie en diep veneuze trombose zijn echter maar heel beperkt gedaan, en gerandomiseerde studies ontbreken volledig. Om deze reden is er grote variatie in de inrichting van de zorgpaden van veneuze trombo-embolie, zowel binnen als tussen de 1e en 2e lijn. Het blijkt dat diagnostiek om complicaties op te sporen beperkt gericht en insufficiënt is. Om richting te geven aan optimale nazorg van veneuze trombo-embolie is er in deze module gekozen om vast te stellen van welke complicaties het vaststaat dat ze de kwaliteit van leven negatief beoordelen. Voor al deze complicaties wordt vervolgens een voorstel gedaan voor de beste manier om deze op te sporen, op basis van beschikbare literatuur en bestaande internationale aanbevelingen.

Search and select

A review of the literature was performed to answer the following question: Do long term complications of venous thromboembolism have an impact on quality of life?

P (patients)	Patients aged ≥ 18 years with venous thrombo-embolism (DVT and/or PE)
I (intervention)	Residual complaints (pain, dyspnea), psychosocial unwellness, post thrombotic syndrome (PTS), chronic thromboembolic pulmonary disease (CTEPD)/pulmonary hypertension
C (comparison)	The absence of residual complaints (pain, dyspnea), no psychosocial unwellness, post thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension (CTEPH)
O (outcome)	Quality of life (QOL)

Definitions of exposure

The working group did define the presence (or absence) of exposure by using the definitions that were used in the study.

Relevant outcome measures

The guideline development group considered general quality of life and/or disease specific quality of life as crucial outcomes for decision making.

For general quality of life: Measured by SF-12 MCS/PCS, SF-36 MCS/PCS, EQ-5D (lower scores indicate poorer QOL for both questionnaires).
For disease specific quality of life: Measured by PEmb-QoL (higher scores indicate poorer QOL) and/or VEINES-QOL/Sym questionnaires (lower scores indicate poorer QOL) and/or CAMPHOR questionnaire (higher scores indicate poorer QOL).

The working group did not define a minimal clinically (patient) important difference for the outcomes. Therefore, definitions of studies were used. If studies did not define a clinically relevant finding default thresholds were used: 0.5SD for continuous outcomes and a 25% difference in relative risk (RR< 0.8 or RR>1.25) for dichotomous outcomes.

The systematic search of ICHOM VTE has been adopted for this search query (search date 8 March 2011- 8 March 2021. All MEDLINE articles have been fully screened by 2 independent members of the ICHOM-VTE taskforce (Gwodz, 2022). The first 20 of the 110 unique non-MEDLINE hits were also viewed. When no new results were found, according to ICHOM-methodology, the point of saturation was reached and no further searches were made. The ICHOM-search query with accompanying PICO was drawn up more broadly than the current search query, which included other outcomes in addition to the outcome quality of life. In addition one study (i.e., the first study, published in 2008) that reported on quality of life in patients with PTS which was not captured by the ICHOM search strategy (search date 2011-2021) and another large study published in 2022 that included a large amount of patients with residual complaints after pulmonary embolism (also not captured by ICHOM as the search date of ICHOM was between 2011-2021) were included. Please note that the methodology that is followed here is a narrative review which cannot be used in the systematic process of rating the quality of the best available evidence as proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group.

Results

A total of 185 studies were initially selected based on the ICHOM search query. Of these 185 studies, n=106 studies were included as they reported on the outcome quality of life (see table in attachments). Since all these studies were considered to fit (at least part of) the PICO, and while there were no resources to systematically review all these studies in this guideline module, it was decided by the working group to select studies that were deemed most relevant for this module (Erickson, 2019; Haig, 2016; Kahn, 2017; Keller, 2019; Ljungqvist, 2018; Roman, 2013; Tabaoda, 2014; Tavoly, 2018). In addition one study (i.e., the first study, published in 2008, (Kahn, 2008) that reported on quality of life in patients with PTS which was not captured by the ICHOM search strategy (search date 2011-2021) and another large study published in 2022 that included a large amount of patients with residual complaints after pulmonary embolism (also not captured by ICHOM as the search date of ICHOM was between 2011-2021, (Valerio, 2022) were included.

The study characteristics are summarized in Table 1 below. Main results are fully shown in the forest plots. Risk of bias assessments are fully shown in the risk of bias table

Tabel 1: Studies included in narrative review.

				Exposure category, VTE with or without:			
Study	**Included in ICHOM**	**Study size, n**	**Condition**	**Psychosocial unwellness**	**Residual complaints**	**PTS**	**CTEPD**
Kahn, 2008	No	387	DVT			X	
Haig, 2016	Yes	209	DVT			X	
Ljungqvist, 2018	Yes	1040	VTE			x	
Kahn, 2017	Yes	100	PE		X		
Keller, 2019	Yes	101	PE		X		
Tavoly, 2018	Yes	203	PE		X		
Valerio, 2022	Yes	1017	PE		x		
Roman, 2013	Yes	156	VTE				X
Taboada, 2014	Yes	42	VTE				X
Erickson, 2019	Yes	907	VTE	X			
Keller, 2019	Yes	101	PE	X			

CTEPD: chronic thromboembolic pulmonary disease; DVT: deep vein thrombosis; PE: pulmonary embolism; PTS: postthrombotic syndrome; VTE: venous thromboembolism

Exposure category PTS

Definitions exposure category

Kahn (2008) and Haig (2016) defined PTS by using the Villalta scale (higher scores indicate more severe PTS). A Villalta score of <5 was considered to represent no PTS.
Ljungqvist (2018) defined PTS by modified Villalta score with a kappa of 0.88 with the original Villalta score. A modified Villalta score of <5 was considered to represent no PTS.

Definitions outcome

Kahn (2008) defined quality of life (QOL) by using the Short-Form Health Survey-36 (SF-36PCS/MCS) and the VEINESQOL/Sym. Clinical relevance was non-defined.
Haig (2016) defined QOL by using the EQ-5D and the VEINES-QOL/Sym questionnaire. A mean difference in in EQ-5D of 0·08 or more was defined as a clinically relevant difference. A mean difference in VEINES-QOL/Sym of four points or more was defined as a clinically relevant difference.
Ljungqvist (2018) defined QOL by SF-36PCS/MCS and the VEINESQOL/Sym. Clinical relevance was non-defined.
Kahn (2008) prospectively measured change in QOL during the two years after a diagnosis of acute DVT at
eight hospitals in Canada. Among the 387 patients recruited, the average age was 56 years. The cumulative incidence of PTS was 47% at two years of follow-up. Patients who developed PTS had lower QOL scores for all questionnaires that were used (Figure 1). Since authors did not define a clinical relevant difference, we used the default threshold ($\geq$ 0.5 SD). By using this threshold, none of the differences reached clinical relevance. The risk of bias was considered as 'some concerns' as it was unclear if excluded participants biased the results and if there was loss to follow-up.

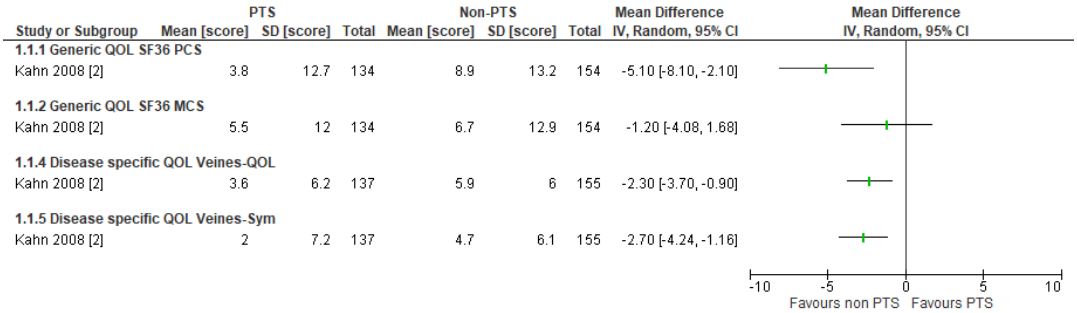

Figure 1: Scores for Quality of life in patients with and without post thrombotic syndrome (PTS, Kahn (2008)). 'Mean' depicted in the forest plot='mean change'. PTS: post thrombotic syndrome.

Haig (2016) included patients who participated in an open-label clinical trial that was designed to evaluate the efficacy and safety of catheter-directed thrombolysis. Patients were aged 18–75 years with acute DVT located higher than the proximal half of the femoral vein. QOL results of intervention and comparator group were pooled after which prognosis of QOL was compared in patients with PTS vs non PTS at 5 years of follow-up. Of 209 enrolled patients, 176 patients were available for analysis (missing data 16%). The average age was 56 years. For analysis on PTS, data was available for 163 patients (missing data 8%). The cumulative incidence of PTS was 63% at 5 years of follow-up. Patients who developed PTS had lower QOL scores for all questionnaires that were used. Outcomes on EQ-5D were 0.71 in PTS vs 0.88 in non-PTS, for VEINES-QOL 47.3 in PTS vs 53.6 in no PTS, for VEINES-Sym 46.6 in PTS vs 54.4 in no PTS. All differences were clinically relevant according to definitions of the study. The risk of bias was considered as 'some concerns' as it was unclear if excluded participants and missing data could have biased the results.

Ljungqvist (2018) conducted a cohort study, including 1040 females with a first episode of VTE. Patients were recruited from the "Thrombo Embolism Hormonal Study" (TEHS), a Swedish nation-wide case-control study on risk factors for venous thromboembolism in females 18-64 years of age. Among the 1040 patients recruited for follow-up, the average age was 49 years. The cumulative incidence of PTS was 20% after a median of six years of follow-up. Patients who developed PTS had lower QOL scores for all questionnaires that were used, *i.e.,*

- -8.6 for SF-36 pcs, P<0.001
- -4.9 for SF-36 mcs, P<0.001
- -8.4 for VEINES/QoL, P<0.001
- -10.6 for VEINES/Sym, P<0.001

Authors did not define a clinical relevant difference. The default threshold (≥ 0.5 SD) could not be used since SDs were not reported. The risk of bias was considered as 'some concerns' as it was unclear if non-participating patients for follow-up biased the results.

Exposure category Chronic thromboembolic pulmonary disease (CTEPD)/pulmonary hypertension (PH)

Definitions exposure category

Roman (2012) defined PH and CTEPD as outpatients aged ≥18 years old who had a clinical diagnosis of PH or CTEPD, without further clarification.

Tabaoda (2012) defined CTEPD as patients with CTEPD and a mean pulmonary artery pressure (PAP) <25 mmHg at baseline that underwent pulmonary endarterectomy (PEA). Date of last venous thromboembolism (VTE) was collected from patient's notes. Time from

last VTE to diagnosis was defined as time from last pulmonary embolism to diagnosis of CTED.

Definitions outcome

Roman (2012) defined health related quality of life (QOL) by using the Short-Form Health Survey-36 (SF-36PCS/MCS) and EQ-5D-5L questionnaire. Clinical relevance was non-defined. Tabaoda (2012) defined health related QOL with the CAMPHOR questionnaire (a measure of health-related QoL for patients with CTEPD). Clinical relevance was non-defined.

Roman (2014) recruited consecutive patients diagnosed with PAH or CTEPH in a multi-center study. Recruitment and data collection for analysis were carried out by a pharmaceutical company (Pfizer). One hundred fifty-six patients completed the evaluation at the baseline visit and 135 (86.5%) completed the end of study visit after six months. Overall, 71% were females, with a mean age of 52 years. N=139 (89%) had PAH and n=17 (11%) had CTEPH. Seventy-six patients (49%) had idiopathic PAH (IPAH) and 23 (17%) had connective tissue disease-associated PAH (CTD-PAH). Twenty percent of patients were diagnosed in the 12 months prior to the start of the study and 80% were diagnosed earlier. Mean scores (+/- SD) for the QoL outcomes are reported in Table 2.

Table 2: Mean scores (SD) for Quality of life in patients with IPAH, CTD-PAH and CTEPD (Roman, 2014).

	IPAH	CTD-PAH	CTEPD
SF-36 PCS	39 (9)	31 (8)	39 (9)
SF-36 MCS	47 (8)	48 (10)	47 (9)
EQ visual analogue scale	59 (21)	53 (17)	65 (17)

IPAH: idiopathic pulmonary arterial hypertension (PAH); CTD-PAH: connective tissue disease-associated PAH; CTEPD: chronic thromboembolic pulmonary disease; PCS: physical component summary; MCS: mental component summary.

The health related QoL score were considered 'worse than those published for the normal population' but references or direct comparisons with the normal population were not provided. Since results were non-compared to a population without PH or CTEPD, we could not determine if findings were clinically relevant. The risk of bias was considered as 'concerns' as there were unclear definitions of the patient population, unclear definitions of exposure, and because recruitment and data collection for analysis were not carried out by the authors.

Tabaoda (2014) screened 1019 patients who underwent PEA at Papworth Hospital. Of those, 42 patients fulfilled the criteria of having CTED. In a before-after study patients were compared with themselves for the outcome health related QoL. Mean age of the patients was 49 years and 60% of the patients were females. 90% of the patients had a documented history of VTE, with a third of patients having more than one episode. All patients were symptomatic, the most frequent symptom was exertional breathlessness and all presented with NYHA functional class II or III limitation.

An improvement in the total score (median [IQR]) and all three domains of the CAMPHOR questionnaire was observed at 6 months and sustained at 1 year; the total score went from 40 (33) at baseline to 11 (30) at six months post-PEA (P<0.001) and 11 (37) at one year post PEA (P<0.001); symptoms went from 15 (13) to 4 (12) (P<0.001) and 5 (12) (P<0.001), respectively; activity went from 10 (9) to 5 (6) (P=0.002) and 4 (11) (P<0.001), respectively; and QoL went from 14 (14) to 2 (11) (P=0.003) and 1 (12) (P=0.001), respectively. Since

results were shown without SDs, we could not use the default threshold (≥ 0.5 SD) to determine if findings were clinically relevant. The risk of bias was considered as 'no concerns'.

Exposure category Residual complaints

Definitions exposure category

Kahn (2017) defined residual complaints by maximal aerobic capacity defined by peak oxygen uptake (Vo2) as a percent of predicted maximal Vo2 (Vo2 peak) on cardiopulmonary exercise testing (CPET) at one year, with < 80% predicted Vo2 peak considered abnormal. CPET was interpreted in real time by a respirologist at each center who was blinded to patient information.

Keller (2018) defined residual complaints by New York Heart Association (NYHA) classes I-IV at six months of follow-up.

Tavoly (2018) defined residual complaints by NYHA class >1 (=persistent dyspnea) after a median follow of 3.6 years.

Valerio (2022) defined residual complaints by post-PE impairment (PPEI). The diagnosis of PPEI required
deterioration in severity, or persistence of the highest severity, of at ≥ 1 'a' (echocardiographic) and ≥ 1 'b' (clinical, functional, or laboratory) parameter/abnormality. Deterioration or persistence was determined
by comparison with the previous visit. For trichotomized (three-level) 'a' or 'b' parameters, the highest severity category was the one defined as 'severe/high'; for dichotomized (two-level) parameters, it was the
'moderate or severe/high' category. Patients were considered to have reached the outcome 'PPEI' if they fulfilled the above criteria at the latest available follow-up visit (3, 12, or 24 months).

Definitions outcome

Kahn (2017) defined health related quality of life (QOL) by using the Short-Form Health Survey-36 (SF-36PCS/MCS). A difference of three points or more was defined as a clinically relevant difference.

Valerio (2022) defined health-related QoL using the EQ-5D-5L questionnaire and its corresponding visual analogue scale. Clinical relevance was non-defined.

Kahn (2017), Keller (2018), Tavoly (2017) and Valerio (2022) defined disease specific QOL by using the PEmb-QOL questionnaire. Clinical relevance was non-defined.

Kahn (2017) recruited out of n=984 patients with acute pulmonary embolism (PE), 100 patients at five hospitals. The average age was 50 years. At 1 year of follow-up, 40 of 86 patients (46%) had percent predicted Vo2 peak < 80% on CPET (i.e., residual complaints). Patients who had residual complaints had lower QOL for all questionnaires that were used. Differences for health related QOL were clinically relevant according to definitions of the study. Since authors could not define a clinical relevant difference for disease specific QOL, we used the default threshold (≥ 0.5 SD). By using this threshold, the difference of for disease specific QOL was also clinically relevant, with some imprecision as confidence intervals were large. The risk of bias was considered as 'some concerns' as it was unclear if excluded participants biased the results.

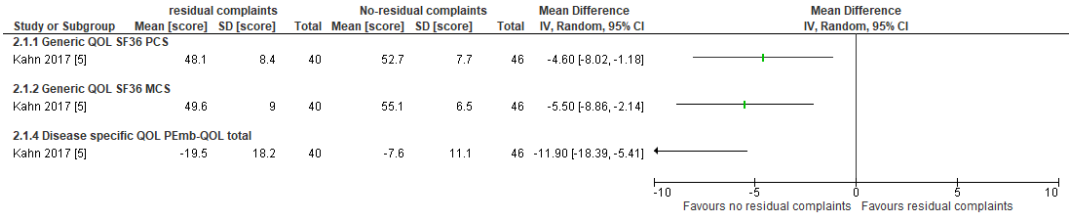

Figure 2: Scores for Quality of life in patients with and without residual complaints (Kahn, 2017).

Keller (2018) recruited out of n=192 patients with acute PE , 101 patients at one outpatient clinic. The median age was 69 years. At six months of follow-up, (47%) had reported persisting dyspnea (NYHA class ≥II; of those, 19 patients (40.4%) were in NYHA class III/IV. Increasing NYHA classes were related to all PEmb-QoL dimensions (see Table 3). authors did not define a clinical relevant difference for disease specific QOL. Since results were shown by regression techniques only (no SDs available) we could not use the default threshold (≥ 0.5 SD) to determine if findings were clinically relevant. The risk of bias was considered as 'some concerns' as it was unclear if excluded participants biased the results.

Table 3: Linear regression models for associations between PEmb-QoL dimensions and residual complaints categorized by NYHA classes at 6-months follow-up (Keller, 2018).

	Dyspnea categorized by NYHA-classes	
	β (95% CI)	**P-value**
Frequency of complaints (FO)	0.5 (0.4-1.1)	<0.001
Activities of daily living limitations (AD)	0.8 (0.6-1.1)	<0.001
Work related problems (WR)	1.2 (0.8-1.5)	<0.001
Social limitations (SL)	0.4 (0.3-0.6)	<0.001
Intensity of complaints (IO)	0.4 (0.3-0.5)	<0.001
Emotional complaints (EC)	0.2 (0.0-0.4)	0.037

CI: confidence interval; NYHA: New York Heart Association

Tavoly (2018) recruited consecutive patients diagnosed with PE in a single center study. After excluding 430 (51%) according to predefined exclusion criteria, 406 patients were found eligible and invited.
Of these, 203 patients completed the PEmb-QoL. After a median follow up of 3.6 (IQR 1.9–6.5) years, 96 (47%) patients reported dyspnea. The PEmb-QoL was higher (i.e., worse) in dyspneic patients (median score 12.5; IQR 9.9-15.0) compared to non-dyspneic patients (median score 8.0; IQR, 7.0-9.5), P<0.005. Since results were shown without SDs, we could not use the default threshold (≥ 0.5 SD) to determine if findings were clinically relevant. The risk of bias was considered as 'some concerns' as it was unclear if excluded participants biased the results.

Valerio (2022) included 1098 patients with PE at 17 study sites. For 81 patients, no follow-up data could be obtained after discharge. In total 880 patients could be assessed for PPEI. The median age was 64 years. At two years of follow-up, 16% had reported PPEI.
Patients who developed PPEI had worse QOL scores for all questionnaires that were used at 2 years of follow-up (Table 4).

Table 4: Scores for Quality of life in patients reporting post pulmonary embolism impairment (PPEI) and patients not reporting PPEI (Tavoly, 2018).

	No PPEI	PPEI	P-value
EQ-5D-L	0.94	0.92	0.3
EQ visual analogue scale	80	70	0.02
PEmb-QoL	9.8%	23.3%	0.003

PPEI: post pulmonary embolism impairment; Pemb-QoL: Pulmonary Embolism Quality of Life Questionnaire

Since results were shown without SDs, we could not use the default threshold (≥ 0.5 SD) to determine if findings were clinically relevant. The risk of bias was considered as 'some concerns' as it was unclear if excluded participants biased the results.

Exposure category Psychosocial unwellness

Definitions exposure category

Erickson (2019) defined psychosocial unwellness as self-reported history of anxiety, or depression at time of enrollment.

Keller (2018) defined psychosocial unwellness as depression as confirmed diagnosis by a physician or administration of antidepressive drugs at 6 months of follow-up.

Definitions outcome

Erickson (2019) defined health related QoL by using the Short-Form Health Survey-12 PCS/MCS. In large national surveys of the entire U.S. population MCS scores have a mean of 50; thus, scores below 50 indicate worse health-related QoL than the typical U.S. person. Clinical relevance was non-defined.

Keller (2018) defined disease specific QOL by using the PEmb-QOL questionnaire. Clinical relevance was non-defined.

Erickson (2019) performed a cross-sectional survey in patients who self-reported VTE within the past two years before study enrollment. Patients diagnosed with cancer within the past two years were excluded. The study sample was recruited by a contract research agency (Hall & Partners, New York, New York, United States). Participants received an industry standard honorarium for their participation. A total of 971 patients accessed and completed the online survey. Data cleaning resulted in 64 patients being removed from the final data. The mean age of survey patients was 52 years, and most were female (57%). Self-reported VTE types were DVT (64%), PE alone (18%), or PE in combination with DVT (18%). The prevalence of anxiety was 27% and for depression 28%. The mean PCS and MCS scores were 41.7 and 46.7. Patients with a prior history of anxiety or depression were more likely to have below average QoL (anxiety 30% vs 16% and depression 33% vs 13% for PCS; anxiety 37% vs 13% and depression 41% vs 13% for MCS, all p-values <0.05). Since results on QoL were compared on an aggregate level (VTE vs the population), we could not determine if findings on anxiety/depression were clinically relevant. Risk of bias was considered as 'concerns' because of unclear definitions of patient population, self-reported definitions of exposure and because recruitment and data collection for analysis were not carried out by the authors.

Keller (2018) recruited out of n=192 patients with acute PE, 101 patients at one outpatient clinic. The median age was 69 years. At six months of follow-up, n=14 (16%) had reported depression. Depression was not consistently associated with QoL assessed by the PEmb-QoL dimensions (point estimate from odds ratios between 1.0 to 2.6), but confidence intervals were wide for which reason it could not be determined if the effects were or were not

clinically relevant. The risk of bias was considered as 'some concerns' as it was unclear if excluded participants biased the results.

Level of evidence of the literature

Summary

From the narrative review of a total of ten studies (from a selection of 106 unselected studies from the ICHOM analysis; Gwodz, 2022) that looked at chronic conditions that can arise after a VTE, the majority of these conditions were associated with a negative quality of life. As shown in Table 5, the prevalence of the chronic conditions was high.

Table 5: Results of the ten studies included in the narrative review, selection of studies from the ICHOM analysis (Gwodz, 2022).

Study	Prevalence exposure	Difference	Statistical significant	Clinically relevant
Kahn, 2008	47%	Yes	Yes	No
Haig, 2016	63%	Yes	Yes	Yes
Ljungqvist, 2018	20%	Yes	Yes	CND
Kahn, 2017	46%	Yes	Yes	Yes
Keller, 2019	47%	Yes	Yes	CND
Tavoly, 2018	47%	Yes	Yes	CND
Valerio, 2022	16%	Yes	Yes	CND
Roman, 2013	CND	Yes	CND	CND
Taboada, 2014	CND	Yes	Yes	CND
Erickson, 2019	27%	CND	CND	CND
Keller, 2019	16%	Imprecise	No	CND

CND: could not be determined; CTEPD: chronic thromboembolic pulmonary disease; DVT: deep vein thrombosis; PE: pulmonary embolism; PTS: postthrombotic syndrome; VTE: venous thromboembolism.

For CTEPD, the prevalence could not be extracted from the studies discussed, but a recent publication has shown that the prevalence of CTEPD is 2-3% (Luijten, 2023). The results from the narrative review could not be assessed using the GRADE methodology, but were consistent and precise within the domains of GRADE (with the exception of the variable psychological unwell-being (Erickson, 2019; Keller, 2019), where numbers were small leading to imprecision), fit within the patient population as defined in the PICO and had the main methodological limitation that due to selection criteria it was not always clear how generalizable the study results are to the total population.

Conclusions

Post thrombotic syndrome (PTS)

No GRADE	PTS may result in a relevant decrease in quality of life as compared to VTE patients without PTS

	Source: Kahn, 2008; Haig, 2016 and Ljungqvist, 2018

Chronic thromboembolic pulmonary disease (CTEPD)

No GRADE	CTEPD may result in a relevant decrease in quality of life as compared to VTE patients without CTEPD *Source: Roman, 2013 and Taboada, 2014*

Residual complaints

No GRADE	Residual complaints may result in a relevant decrease in quality of life as compared to VTE patients without residual complaints *Source: Kahn, 2017; Keller, 2019; Tavoli, 2018 and Valerio, 2022*

Psychosocial unwellness

No GRADE	Psychosocial unwellness may result in a relevant decrease in quality of life as compared to VTE patients without psychosocial unwellness, but the evidence is uncertain *Source: Erickson, 2019 and Keller, 2019*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Deze module is gebaseerd op het sterke bewijs van de impact van verschillende lange termijn complicaties van veneuze trombo-embolie. Dit bewijs is verzameld in observationeel onderzoek, voornamelijk uitgevoerd in Nederland, Canada en Scandinavië. In de uiteindelijke aanbeveling wordt dit bewijs in een context geplaatst die aansluit op de dagelijkse praktijk. Het is ondoenlijk om voor alle mogelijke aanhoudende symptomen een aparte PICO te schrijven en tot een evidence based advies te komen over de te volgen strategie. Daarom is gekozen gebruik te maken van (inter)nationale consensus en recente internationale richtlijnen over het te voeren beleid (Delcroix, 2021; Humbert, 2022; Klok, 2022; Konstantinides, 2022).

Uit de narratieve review van in totaal tien studies (uit een selectie van 106 ongeselecteerde studies uit de ICHOM-analyse (Gwodz, 2022) die keken naar chronische aandoeningen die kunnen ontstaan na een VTE, bleek dat het merendeel van deze aandoeningen consistent geassocieerd is met mindere kwaliteit van leven. De studies gaven niet genoeg informatie om te toetsen of dit verschil ook klinisch relevant is (Tabel 5).

Post trombotisch syndroom (PTS)

Ongeveer 10 tot 50% van de patiënten die een DVT heeft doorgemaakt zal een PTS ontwikkelen (ten Cate-Hoek, 2018). Hierbij is de incidentie één jaar na DVT ongeveer 10% en dit neemt toe tot 50% in de periode van vijf tot acht jaar na DVT. De incidentie van ernstige PTS (veneus ulcus) is 1-2%. Het klinisch beeld van PTS is variabel. Patiënten kunnen pijn, een zwaar gevoel, zwelling, kramp, paresthesiën en of jeuk ervaren. De symptomen kunnen continu of intermitterend zijn en verbeteren in rust en bij omhoog leggen van het been. Ook kan er sprake zijn van veneuze claudicatio. De patiënt ervaart dit typisch bij sneller lopen, traplopen of bergop lopen. De diagnose PTS wordt gesteld met behulp van de Villalta score, die tenminste zes maanden na de oorspronkelijke diagnose vijf punten of meer moet zijn. Een deel van de score betreft zelf-gerapporteerde symptomen. Het is aan te bevelen in ieder geval na een periode van drie maanden de Villalte score samen met patiënt te berekenen.

De initiële behandeling van PTS bestaat uit compressietherapie en bewegingsadviezen. Zie verder ook de richtlijn van de European Society for Vascular Surgery (ESVS). Patiënten met een hoge ziektelast die veel beperkingen ervaren kunnen worden verwezen naar een expertisecentrum.

CTEPD/CTEPH en aanhoudende klachten van benauwdheid

Voor CTEPH/CTEPD kon de prevalentie niet uit de besproken studies gehaald worden, maar een recente publicatie heeft aangetoond dat de prevalentie van CTEPH 2-3% is, net als dat van CTEPD (Held, 2023; Luijten, 2023). CTEPH en CTEPD worden gedefinieerd als de aanwezigheid van reststolsels in de pulmonaal arteriën ondanks ten minste drie maanden antistolling (met morfologie van een chronisch stolsel, zoals een zogenaamd webje) met perfusie defecten en pulmonale hypertensie (CTEPH), ofwel gepaard gaande met symptomen van benauwdheid of inspanningsbeperking én meetbare fysiologische afwijkingen zoals dode-ruimte ventilatie of pulmonale hypertensie bij inspanning (CTEPD) (Humbert, 2022). Het is aangetoond dat een vroege diagnose van CTEPH (binnen maanden na de longembolie) resulteert in snellere behandeling en een betere overleving (Klok, 2017). Het blijkt echter dat door gebrek aan gestandaardiseerde follow-up van patiënten met een longembolie en een gebrek aan gedetailleerde kennis van dit ziektebeeld bij behandelaren de diagnostische vertraging in Nederland gemiddeld twee jaar is (Ende-verhaar, 2018). Verschillende studies laten zien dat het implementeren van een algoritme gericht op CTEPH inderdaad resulteert in een duidelijke verkorting van de diagnostische vertraging (Boon, 2021; Valerio, 2022). Zo'n algoritme begint met het op een gestandaardiseerde manier vaststellen van aanhoudende klachten, bijvoorbeeld met een PROM (Konstantinides, 2020, Klok, 2022). Een goed voorbeelden daarvan is de modified Medical Research Council Dyspnoe vragenlijst (mMRC). Patiënten met klachten verdienen aanvullend onderzoek. Het onderzoek van keuze bij verdenking op pulmonale hypertensie is een echocardiografie. Het is gebleken dat een normale ECG en (NT-pro) BNP bloedtest de aanwezigheid van pulmonale hypertensie zeer onwaarschijnlijk maakt (Boon, 2021; Humbert, 2022). Met deze tussenstap kan het aantal verwijzingen voor een echocardiografie beperkt worden. Bij aanhoudende benauwdheid maar geen pulmonale hypertensie is een CPET de diagnostische test van keus. Hiermee kan onderscheid gemaakt worden tussen verschillende oorzaken van benauwdheid, en tevens aanwijzingen voor CTEPD worden gevonden, bijvoorbeeld als er sprake is van dode ruimte ventilatie. Zowel patiënten met echografische verdenking op pulmonale hypertensie als verdenking op CTEPD op basis van de CPET hebben een indicatie voor nieuwe beeldvorming van de pulmonaal vaten en perfusie (Humbert, 2022; Konstantinides, 2020). Dat kan met een CT scan of nucleaire scan. Indien op basis van deze beeldvorming de verdenking op CTEPH of CTEPD blijft bestaan, horen patiënten doorverwezen te worden naar een CTEPH expertise centrum. Adequate behandeling resulteert gemiddeld in een sterke verbetering van de kwaliteit van leven.

Patiënten met aanhoudende benauwdheid en/of inspanningsbeperking waarbij CTEPH/CTEPD is uitgesloten, hebben baat bij hart/long revalidatie (Boon/Janssen, 2021; Klok, 2022 and Jervan, 2023): de ervaringen beperkingen in het dagelijks leven nemen gemiddeld af en de kwaliteit van leven neemt toe.

Psychosociale complicaties

Erickson (2019) en Keller (2019) definieerden psychosociale complicaties als angst en depressie, en concluderen dat deze toestand kan leiden tot een relevante daling van de kwaliteit van leven. Ook voor angst en depressie bestaan bruikbare en gevalideerde PROMs. Een voorbeeld hiervan is de Vierdimensionale Klachtenlijst (4DKL). De 4DKL is een vragenlijst bestaande uit 50 items, gericht op psychosociale klachten. De lijst is ontwikkeld in de huisartsenpraktijk en maakt onderscheid tussen aspecifieke 'distress'-klachten, depressie,

angst, en somatisatie. Deze vier symptoomdimensies vormen tevens de vier verschillende categorieën. De antwoordmogelijkheden van de lijst zijn ordinaal opgebouwd en hoe hoger een patiënt scoort op de vragenlijst, des te meer psychosociale klachten ondervindt hij in zijn dagelijkse handelingen. Met de 4DKL kunnen problemen in de genoemde dimensies worden opgespoord en het geeft handvatten voor de noodzaak tot nadere diagnostiek. Een alternatieve PROM is de "Hospital Anxiety and Depression Scale" HADS. De HADS meet kernklachten van angst en depressie zonder daarbij lichamelijke klachten te betrekken. Het is een korte vragenlijst, die gemakkelijk te gebruiken is. De schaal gaat in op gevoelens in de afgelopen vier weken en bestaat uit een angstschaal en een depressieschaal met beide zeven items. Hoe hoger een patiënt scoort op deze vragenlijst des te meer klachten hij/zij ervaart.

Internationale consensus

De 2019 ESC/ERS longembolie richtlijn suggereert gebruik te maken van PROMS om te bepalen bij welke patiënten aanvullend onderzoek naar CTEPH geïndiceerd is (Konstantinides, 2020). Het in 2022 gepubliceerde ESC/ERS consensus document over follow-up na acute longembolie is wat specifieker op dit onderwerp en adviseert naast een PROM voor dyspnoe ook een PROM voor het vaststellen van functionele beperkingen voor. Dit helpt bij het inschatten van de ernst van aanhoudende symptomen maar ook om de potentiële impact van een behandeling in te schatten. De Post-VTE Functionele Status (PVFS) schaal richt zich op relevante aspecten van het dagelijks leven in de eerste periode na een VTE-diagnose (Boon, 2020). Het is bedoeld om de zorgmedewerker en patiënt bewust te maken van goed of minder goed herstel van VTE en de gevolgen daarvan op het functioneren van de patiënt. Minder goed herstel kan wijzen op lange termijn complicaties die behandeling behoeven. De PVFS-schaal is ordinaal en heeft zes klassen die variëren van nul (geen symptomen) tot vijf (dood, D). De schaal bestrijkt het gehele spectrum aan functionele uitkomsten door zich te richten op zowel beperkingen in gebruikelijke taken/activiteiten in de thuissituatie, op het werk of de studie, als op veranderingen in levensstijl. De klassen van de PVFS-schaal zijn intuïtief en kunnen gemakkelijk worden
beoordeeld en vervolgens worden geïnterpreteerd door artsen en patiënten.
Een internationale werkgroep van zorgmedewerkers en patiënten heeft zich gericht op het vaststellen van de kernuitkomsten van veneuze trombo-embolie die voor alle patiënten relevant zijn: ICHOM-VTE (Gwodz, 2022). Nadat de kernuitkomsten waren vastgesteld, werd er voor elke uitkomst een instrument bepaald, met als belangrijkste kenmerk dat deze zo mogelijk patiëntgerapporteerd, gevalideerd, makkelijk (en gratis) in veel talen beschikbaar en toegankelijk is. In deze uitkomst set zitten PROMS voor kwaliteit van leven, pijn, benauwdheid, angst, depressie, functionele beperkingen, patiënttevredenheid en verandering van levensvisie. Om het aantal in te vullen vragen te beperken heeft de set enkele cascade opties ingebouwd.
De internationale vereniging voor trombose en hemostase (ISTH) heeft in recente publicaties de relevantie van het gebruik van PROMS bevestigd, en onderschrijft de relevantie van de ICHOM set (de Jong, 2023).

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

In deze module staat de kwaliteit van leven van de patiënt centraal. De ICHOM-set die wordt besproken, is ontwikkeld met en voor patiënten. Hierbij was ook een Nederlandse patiëntpartner betrokken. In de follow-up is het voor patienten belangrijk dat er goede informatie gegeven wordt over de aandoening en ook (de inhoud van) het nazorgtraject. Ook dient duidelijk te zijn wie het aanspreekpunt is bij eventuele vragen vanuit de patient.

Kosten (middelenbeslag)

Er is nauwelijks tot geen onderzoek voor handen naar de kosteneffectiviteit van (PROMS gestuurde) symptoom gerichte follow-up na VTE. Wel is er een Nederlandse analyse die aantoont dat eerdere diagnose van CTEPH na longembolie kosteneffectief is (Boon/ Van den Hout, 2021). Het is mogelijk dat gestandaardiseerde nazorg van veneuze trombo-embolie overdiagnostiek voorkomt, en leidt tot gerichte verwijzingen. Het gebruik van PROMS is kosteloos, al moet er wel worden geïnvesteerd in patiënten motivatie/instructie en een (liefst digitale) manier om de PROMS uitkomsten te verwerken en op te slaan. Een gestandaardiseerde en gestructureerde nazorg van VTE patiënten is mogelijk doelmatig en voorkomt onnodige zorg (Ende-Verhaar, 2018).

Aanvaardbaarheid, haalbaarheid en implementatie

Het implementeren van PROMS kan lastig zijn. Niet alleen moeten de juiste PROMS worden gekozen, ook moeten er juiste instructie aan patiënten én zorgmedewerkers komen, en is een infrastructuur voor de invullen, opslaan en verwerken van de PROM resultaten noodzakelijk. Het bespreken van PROM uitslagen kost tijd, al kan het ook versnellend werken omdat een deel van de anamnese reeds ondervangen is. Er is een PROM toolbox samengesteld door het Zorginstituut die houvast kan geven. De PROM-toolbox bestaat uit de PROM-wijzer en de PROM-cyclus. De PROM-wijzer gaat over de oriëntatie en voorbereiding op het gebruik van PROMs. De PROM-cyclus gaat over de selectie en toepassing van PROMs.

Aanbeveling

Om richting te geven aan de optimale nazorg van patiënten met een VTE heeft de werkgroep vastgesteld welke complicaties de kwaliteit van leven na een VTE negatief beïnvloeden, namelijk PTS, CTEPH/CTEPH en psychosociale complicaties. De werkgroep acht het van belang dat er in de nazorg voor de patiënten met een VTE aandacht wordt gegeven aan tenminste deze complicaties, bijvoorbeeld tijdens het drie maanden follow-up moment. Op basis van beschikbare literatuur en bestaande (recente) internationale richtlijnen zijn er aanbevelingen opgesteld hoe deze complicaties opgespoord kunnen worden en wat mogelijke vervolgstappen zijn.

Standaardiseer de follow-up van veneuze trombo-embolie om een goed en volledig beeld te krijgen van de aanwezigheid van de in deze module beschreven relevante complicaties van veneuze trombo-embolie die de kwaliteit van leven negatief beïnvloeden: PTS (na DVT), CTEPH/CTEPH (na longembolie) en psychosociale complicaties.

- Een goede timing hiervoor is rond het drie maanden follow-up moment.
- Geef ten minimale aandacht aan functionele beperkingen, benauwdheid en psychosociale impact, en - bij patiënten met een diep veneuze trombose – het post trombotisch syndroom.
- Maak hiervoor bij voorkeur gebruik van PROMS en de Villalta score: daarmee worden deze symptomen reproduceerbaar en zo objectief mogelijk vastgelegd, en kan beloop ervan door de tijd en de effecten van behandeling goed worden gemonitord.

Patiënten met PTS

Behandel patiënten met aangetoonde PTS initieel met compressietherapie en bewegingstherapie.

Patiënten die aanhoudend benauwd zijn of inspanningsbeperking hebben

Voer aanvullende diagnostiek uit om chronische trombo-embolische pulmonale hypertensie/ziekte (CTEPH/CTEPD) uit te sluiten en volg hierbij de volgende stappen, namelijk:

1. Verricht eerst een ECG en (NT-pro) BNP bloedtest of een echocardiografie ;
2. Indien er geen aanwijzingen zijn voor pulmonale hypertensie: voer een cardiopulmonale inspanningstest (CPET) uit.
3. Indien er aanwijzingen zijn voor CTEPH/CTEPD bij echocardiografie of CPET: beeldvorming van de pulmonale vaatboom/perfusie is geïndiceerd;
    - Verwijs patiënten met CTEPH/CTEPD door naar een expertisecentrum.
    - Indien er geen sprake is van CTEPH/CTEPH: overweeg om cardiopulmonale revalidatie in te zetten.

Patiënten met een vastgestelde relevante angststoornis of depressie

- Zet een adequate behandeling in, bij voorkeur via de eerste lijn.

Kennisvragen

Het is onbekend welke (combinatie van) PROMS het meest past in de follow-up van patiënten met veneuze trombo-embolie. In de ICHOM set werd er gekeken naar de beste PROM per kern uitkomst, waardoor er veel overlap is tussen de aanbevolen PROMS, en er veel vragen (dubbel) moeten worden beantwoord. Studies naar de impact van PROM-gestuurde follow-up bij veneuze trombo-embolie ontbreken, evenals studies naar de optimale revalidatie strategie bij longembolie patiënten met persisterende klachten bij wie CTEPH/CTEPD uitgesloten is. Ook de veiligheid en effectiviteit van revascularisatie interventies bij PTS zijn onvoldoende bekend.

Het gaat dus om de volgende kennisvragen:

- Welke (combinaties van) PROMS zijn het meest passend in de follow-up van patiënten met een veneuze trombo-embolie?
- Wat is de optimale revalidatie strategie bij patiënten met een longembolie met persisterende klachten, bij wie CTEPH/CTEPD is uitgesloten?
- Wat is de veiligheid en effectiviteit van re vascularisatie-interventies bij patiënten met post-trombotisch syndroom en CTEPD/CTEPH?

Literatuur

Boon GJAM, Barco S, Bertoletti L, et al. Measuring functional limitations after venous thromboembolism: Optimization of the Post-VTE Functional Status (PVFS) Scale. Thromb Res. 2020;190:45-51. doi:10.1016/j.thromres.2020.03.020

Boon GJAM, Ende-Verhaar YM, Bavalia R, et al. Non-invasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II study. Thorax. 2021;76(10):1002-1009. doi:10.1136/thoraxjnl-2020-216324

Boon GJAM, Janssen SMJ, Barco S, et al. Efficacy and safety of a 12-week outpatient pulmonary rehabilitation program in Post-PE Syndrome. Thromb Res. 2021;206:66-75. doi:10.1016/j.thromres.2021.08.012

Boon GJAM, van den Hout WB, Barco S, et al. A model for estimating the health economic impact of earlier diagnosis of chronic thromboembolic pulmonary hypertension. ERJ Open Res. 2021;7(3):00719-2020. Published 2021 Sep 6. doi:10.1183/23120541.00719-2020

Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. Eur Respir J. 2021;57(6):2002828. Published 2021 Jun 17. doi:10.1183/13993003.02828-2020

Ende-Verhaar YM, van den Hout WB, Bogaard HJ, et al. Healthcare utilization in chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost. 2018;16(11):2168-2174. doi:10.1111/jth.14266

Erickson RM, Feehan M, Munger MA, Tak C, Witt DM. Understanding Factors Associated with Quality of Life in Patients with Venous Thromboembolism. Thromb Haemost. 2019;119(11):1869-1876. doi:10.1055/s-0039-1696717

Gwozdz AM, de Jong CMM, Fialho LS, et al. Development of an international standard set of outcome measures for patients with venous thromboembolism: an International Consortium for Health Outcomes Measurement consensus recommendation. *Lancet Haematol*. 2022;9(9):e698-e706. doi:10.1016/S2352-3026(22)00215-0

Haig Y, Enden T, Grøtta O, et al. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. Lancet Haematol. 2016;3(2):e64-e71. doi:10.1016/S2352-3026(15)00248-3

Held M, Pfeuffer-Jovic E, Wilkens H, et al. Frequency and characterization of CTEPH and CTEPD according to the mPAP threshold > 20 mm Hg: Retrospective analysis from data of a prospective PE aftercare program. Respir Med. 2023;210:107177. doi:10.1016/j.rmed.2023.107177

Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension [published correction appears in Eur Heart J. 2023 Apr 17;44(15):1312]. Eur Heart J. 2022;43(38):3618-3731. doi:10.1093/eurheartj/ehac237

Jervan Ø, Haukeland-Parker S, Gleditsch J, et al. The Effects of Exercise Training in Patients With Persistent Dyspnea Following Pulmonary Embolism: A Randomized Controlled Trial. Chest. 2023;164(4):981-991. doi:10.1016/j.chest.2023.04.042

de Jong CMM, de Wit K, Black SA, et al. Use of patient-reported outcome measures in patients with venous thromboembolism: communication from the ISTH SSC Subcommittee on Predictive and Diagnostic Variables in Thrombotic Disease. J Thromb Haemost. 2023;21(10):2953-2962. doi:10.1016/j.jtha.2023.06.023

Kahn SR, Shbaklo H, Lamping DL, et al. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. J Thromb Haemost. 2008;6(7):1105-1112. doi:10.1111/j.1538-7836.2008.03002.x

Kahn SR, Hirsch AM, Akaberi A, et al. Functional and Exercise Limitations After a First Episode of Pulmonary Embolism: Results of the ELOPE Prospective Cohort Study. Chest. 2017;151(5):1058-1068. doi:10.1016/j.chest.2016.11.030

Keller K, Tesche C, Gerhold-Ay A, et al. Quality of life and functional limitations after pulmonary embolism and its prognostic relevance. J Thromb Haemost. 2019;17(11):1923-1934. doi:10.1111/jth.14589

Klok FA, Huisman MV. Management of incidental pulmonary embolism. Eur Respir J. 2017;49(6):1700275. Published 2017 Jun 29. doi:10.1183/13993003.00275-2017

Klok FA, Ageno W, Ay C, et al. Optimal follow-up after acute pulmonary embolism: a position paper of the European Society of Cardiology Working Group on Pulmonary Circulation and Right Ventricular Function, in collaboration with the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology, endorsed by the European Respiratory Society. Eur Heart J. 2022;43(3):183-189. doi:10.1093/eurheartj/ehab816

Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543-603. doi:10.1093/eurheartj/ehz405

Ljungqvist M, Holmström M, Kieler H, Lärfars G. Long-term quality of life and postthrombotic syndrome in women after an episode of venous thromboembolism. Phlebology. 2018;33(4):234-241. doi:10.1177/0268355517698620

Luijten D, Talerico R, Barco S, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: an updated systematic review and meta-analysis. Eur Respir J. 2023;62(1):2300449. Published 2023 Jul 7. doi:10.1183/13993003.00449-2023

Roman A, Barbera JA, Castillo MJ, Muñoz R, Escribano P. Health-related quality of life in a national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. Arch Bronconeumol. 2013;49(5):181-188. doi:10.1016/j.arbres.2012.12.007

Taboada D, Pepke-Zaba J, Jenkins DP, et al. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. Eur Respir J. 2014;44(6):1635-1645. doi:10.1183/09031936.00050114

Tavoly M, Wik HS, Sirnes PA, et al. The impact of post-pulmonary embolism syndrome and its possible determinants. Thromb Res. 2018;171:84-91. doi:10.1016/j.thromres.2018.09.048

Ten Cate-Hoek AJ. Diagnosis and prevention of the post-thrombotic syndrome. Ned Tijdschr Hematol. 2018;15:319-25

Valerio L, Mavromanoli AC, Barco S, et al. Chronic thromboembolic pulmonary hypertension and impairment after pulmonary embolism: the FOCUS study. Eur Heart J. 2022;43(36):3387-3398. doi:10.1093/eurheartj/ehac206

Bijlagen bij module follow-up VTE

Implementatietabel

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	Sterkte van de aanbeveling	Bewijskracht per uitkomstmaat	Verkeerslicht per (sub)aanbeveling

Standaardiseer de follow-up van veneuze trombo-embolie om een goed en volledig beeld te krijgen van de aanwezigheid van de in deze module beschreven relevante complicaties van veneuze trombo-embolie die de kwaliteit van leven negatief beïnvloeden: PTS (na DVT), CTEPH/CTEPH (na longembolie) en psychosociale complicaties. • Een goede timing hiervoor is rond het drie maanden follow-up moment. • Geef ten minimale aandacht aan functionele beperkingen, benauwdheid en psychosociale impact, en - bij patiënten met een diep veneuze trombose – het post trombotisch syndroom. • Maak hiervoor bij voorkeur gebruik van PROMS en de Villalta score: daarmee worden deze symptomen reproduceerbaar en zo objectief mogelijk vastgelegd, en kan beloop ervan door de tijd en de effecten van behandeling goed worden gemonitord. *Patiënten met PTS* Behandel patiënten met aangetoonde PTS initieel met compressietherapie en bewegingstherapie. *Patiënten die aanhoudend benauwd zijn of inspanningsbeperking hebben* Voer aanvullende diagnostiek uit om	**X** Sterk (doe/ gebruik) / □ Zwak (overweeg)	**Overall bewijskracht** □ **H** □ **M** □ **L** □ **VL** □ **NG** **Range bewijskracht van alle uitkomstmaten** □ **H** □ **M** □ **L** □ **VL** □ **NG** **OF** **X voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in □ **ORANJE:** gebruik tabel B ***X*** **LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in

chronische trombo-embolische pulmonale hypertensie/ziekte (CTEPH/CTEPD) uit te sluiten en volg hierbij de volgende stappen, namelijk: 1. Verricht eerst een ECG en (NT-pro) BNP bloedtest of een echocardiografie ; 2. Indien er geen aanwijzingen zijn voor pulmonale hypertensie: voer een cardiopulmonale inspanningstest (CPET) uit. 3. Indien er aanwijzingen zijn voor CTEPH/CTEPD bij echocardiografie of CPET: beeldvorming van de pulmonale vaatboom/perfusie is geïndiceerd. a. Verwijs patiënten met CTEPH/CTEPD door naar een expertisecentrum. b. Indien er geen sprake is van CTEPH/CTEPH: overweeg om cardiopulmonale revalidatie in te zetten. *Patiënten met een vastgestelde relevante angststoornis of depressie* Zet een adequate behandeling in, bij voorkeur via de eerste lijn.			

Implementatietabel

Tabel A: (De-)Implementatietabel met impuls analyse

Aanbeveling			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**X Ongewenste praktijkvariatie** **X Nieuwe evidentie** □ **Anders** **Toelichting:** De follow-up van VTE vindt plaats in de 1e en 2e lijn, en door verschillende medisch specialisten/verpleegkundigen. Het gebrek aan richtlijnen resulteert in een grote praktijk variatie, inefficiënte inzet van middelen en een lange diagnostische vertraging van de meest ernstige lange termijn complicaties. Tevens is er beperkt/geen aandacht voor de psychosociale impact van een VTE diagnose.		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	□ < **1000** □ < **5000** ***X*** **5000-40.000 per jaar** □ **> 40.000**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	□ **Ja**: hoe verhoudt deze aanbeveling zich tot de andere aanbevelingen uit deze module/ richtlijn of uit andere richtlijnen(modules)? Dient hier rekening mee gehouden te worden bij de implementatie of kan dit worden gezien als een losstaande aanbeveling? **Toelichting:** [toelichting] **X Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	Het implementeren van standaard gebruik van PROMS vergt inspanning en er zijn kosten aan verbonden. Een addendum op de	Er is veel internationale aandacht voor met name vroegdiagnostiek van CTEPH en psychosociale impact van VTE. Het is

		nieuwe NHG-Standaard zal nodig zijn.	onwaarschijnlijk dat de aanbevelingen op korte termijn achterhaald zullen zijn.
b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	Het implementeren van standaard gebruik van PROMS vergt inspanning en er zijn kosten aan verbonden. De mate van bewijs is in zo verre beperkt dat er geen RCTs zijn op dit onderwerp, en er ook nooit zullen komen. De vraag is dus of de zorgverleners overtuigd zullen raken om zich in te zetten de aanbevelingen te volgen.	Goed onderwijs op dit gebied. Steeds meer aandacht hiervoor in de internationale richtlijnen.
c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	Het vergt een inspanning van patiënten om vragenlijsten in te vullen.	De aanbevelingen zijn bedoeld om de nazorg voor de individuele patiënt te verbeteren en persoonlijker te maken. Een goede uitleg van het doel en nut van de vragenlijst zal de patiënt juist het gevoel geven serieus genomen te worden.
d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	-	-
e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	Het implementeren van standaard gebruik van o.a. PROMS vergt inspanning en er zijn kosten aan verbonden.	ICT-ondersteuning, aanpassing van PGO's voor VTE.

f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	Dit kost een grotere inspanning van zowel de zorgverlener als de patiënt.	Goed onderwijs, implementatieondersteuning door de zorgverzekeraars. Op maatschappelijk niveau zal het implementeren van de aanbevelingen leiden tot een kostenbesparing en betere zorguitkomsten (meer QALYs).

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	**X** Patiënt/ cliënt (naaste) **X** Professional **X** Beroepsvereniging **X** Ziekenhuis(bestuurder) □ Zorgverzekeraars/ NZa □ Zorginstituut [duiding nodig]
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	Uitleg over het belang van het invullen van de vragenlijsten op door de belangrijkste informatiebronnen voor patiënten (Harteraad, Trombosestichting etc.). Wellicht dat 1 nationale informatiebron waar alle andere uit kunnen putten een stap voorwaarts zou kunnen zijn. Daarnaast is het belangrijk dat er in het onderwijs aandacht wordt gegeven aan dit onderwerp en dat de passende ICT-ondersteuning beschikbaar is.
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	□ < 1 jaar □ < 2 jaar **X** < 3 jaar
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	**X Ja*** □ **Nee** **Toelichting:** Zoals eerder vermeld zal er een aanpassing nodig zijn van de NHG-Standaard om de aanbevelingen ook in de eerste lijn te implementeren. Alleen het publiceren van deze richtlijn zal niet voldoende verandering teweeg brengen. Het is onzeker of de aanbeveling op de Implementatie Agenda geplaatst zou moeten worden.

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

Risk of bias table for cohort studies based on risk of bias tool by the CLARITY Group at McMaster University

Author, year	**Selection of participants** **Was selection of exposed and non-exposed cohorts drawn from the same population?**	**Exposure** **Can we be confident in the assessment of exposure?**	**Outcome of interest** **Can we be confident that the outcome of interest was not present at start of study?**	**Confounding-assessment** **Can we be confident in the assessment of confounding factors?**	**Confounding-analysis** **Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables?**	**Assessment of outcome** **Can we be confident in the assessment of outcome?**	**Follow up** **Was the follow up of cohorts adequate? In particular, was outcome data complete or imputed?**	**Co-interventions** **Were co-interventions similar between groups?**	**Overall Risk of bias**
	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Low, Some concerns, High
Kahn, 2008	Probably yes	Probably yes	Not applicable	Not applicable	Not applicable	Definitely yes	Probably yes	Not applicable	**Some concerns**

	Reason: Participants were selected consecutively from outpatienst clinics, but there were exclusion criteria.	Reason: questionnaire data with ascertainment rules were used.	Reason: Outcome concerned quality of life	Reason: The stdy design was prognostic	Reason: The stdy design was prognostic	Reason: validated questionnaire data with ascertainment rules were used.	Reason: Follow up was up to 2 years after acute DVT. Of 387 enrolled participants, 260 attended the final visit. Cumulative incidences were obtained through Kaplan Meier, suggesting that censoring at a calendar end date. took place No loss to follow-up was described	Reason: The stdy design was prognostic	**Unclear if excluded participants biased the results. Unclear if there was loss to follow-up**
Haig, 2016	Probably yes Reason: participants from an open label clinical trial were included. There were some dropouts over 5 year follow-up	Probably yes Reason: questionnaire data with ascertainment rules were used.	Not applicable Reason: Outcome concerned quality of life	Not applicable Reason: The study design was prognostic	Not applicable Reason: The study design was prognostic	Definitely yes Reason: validated questionnaire data with ascertainment rules were used.	Probably yes Reason: follow up was up to 5 years after acute DVT. Of 209 enrolled patients, 176 patients were available for analysis (missing data 16%). For analysis on PTS, data was	Not applicable Reason: The stdy design was prognostic	**Some concerns** **Unclear if excluded participants biased the results. Missing data nearing 20% of total**

							available for 163 patients (missing data 8%).		
Ljunqvist, 2018	Probably yes Reason: Participants were selected from outpatienst clinics, through consent. For follow-up approximately 25% did not consent or provided information needed for follow-up	Probably yes Reason: questionnaire data with ascertainment rules were used.	Not applicable Reason: Outcome concerned quality of life	Not applicable Reason: Outcome concerned quality of life	Not applicable Reason: The stdy design was prognostic	Definitely yes Reason: validated questionnaire data with ascertainment rules were used.	Probably yes Reason: Median follow was 6 years after VTE. Of 1050 enrolled patients, 1040 patients were available for analysis (missing data n=10) patients (missing data 8%).	Not applicable Reason: The study design was prognostic	**Some concerns** **Unclear if excluded participants (nearing 25% of total) biased the results.**
Kahn, 2017	Probably yes Reason: Participants were selected consecutively from outpatient clinics, but there were exclusion	Definitely yes Reason: Objective measures were used (maximal Vo2) on cardiopulmonary exercise testing (CPET)and interpreted in real time by a	Not applicable Reason: Outcome concerned quality of life	Not applicable Reason: The study design was prognostic	Not applicable Reason: The study design was prognostic	Definitely yes Reason: validated questionnaire data with ascertainment rules were used.	Probably yes Reason: Follow up was up to 1 year after acute PE.	Not applicable Reason: The study design was prognostic	**Some concerns** **Unclear if excluded participants biased the results.**

		respirologist at who was blinded to patient information.							
Keller, 2018	Probably yes Reason: Participants were selected consecutively from one outpatient clinic (n=192), but there were exclusion criteria	Definitely yes Reason: Objective measures were used.	Not applicable Reason: Outcome concerned quality of life	Not applicable Reason: The study design was prognostic	Not applicable Reason: The study design was prognostic	Definitely yes Reason: validated questionnaire data with ascertainment rules was used.	Probably yes Reason: Follow up was up to 0.5 years after acute PE.	Not applicable Reason: The study design was prognostic	**Some concerns** **Unclear if excluded participants biased the results.**
Tavoly, 2018	Probably yes Reason: Participants were selected consecutively from one outpatient clinic, but there were exclusion criteria (and not all participated.	Definitely yes Reason: Objective measures were used.	Not applicable Reason: Outcome concerned quality of life	Not applicable Reason: The study design was prognostic	Not applicable Reason: The study design was prognostic	Definitely yes Reason: validated questionnaire data with ascertainment rules was used.	Probably yes Reason: Median Follow up was 3.6 years after acute PE.	Not applicable Reason: The study design was prognostic	**Some concerns** **Unclear if excluded participants biased the results.**
Valerio, 2022	Probably yes Reason: The FOCUS	Definitely yes Reason: Objective	Not applicable Reason: Outcome	Not applicable	Not applicable	Definitely yes Reason: validated	Probably yes Reason: Maximum	Not applicable	**Some concerns**

	prospectively enrolled consecutive unselected patients with confirmed diagnosis of acute symptomatic PE. The study was performed at 17 hospitals in Germany. Patients were excluded if the diagnosis of PE was an incidental finding during diagnostic work up for another disease; if they had A documented history of confirmed CTEPH; or if they had already been enrolled in this study in the past	measures were used.	concerned quality of life	Reason: The study design was prognostic	Reason: The study design was prognostic	questionnaire data with ascertainment rules was used.	Follow up was 2 years after acute PE. Of 1098 patienmts included 81 patienst did not provide follow-up data (7%). PPEI could be evaluated in 880 patients	Reason: The study design was prognostic	**Unclear if missing data biased the results.**
Roman, 2012	Unclear	Definitely no	Not applicable	Not applicable	Not applicable	Definitely yes	Probably yes	Not applicable	**Concerns. Unclear**

	Reason: consecutive patients diagnosed with PAH or CTEPH in a multi-center study, further undefined.	Reason: the exposure was not defined	Reason: Outcome concerned quality of life	Reason: The study design was prognostic	Reason: The study design was prognostic	Reason: validated questionnaire data with ascertainment rules was used.	Reason: Follow up was 6 months. Of 156 patients included 21 patienst did not provide follow-up data (13%).	Reason: The study design was prognostic	**definitions of patient population, unclear definitions of exposure. Recruitment and data collection for analysis were not carried out by the authors**
Tabaoda, 2014	Probably yes Authors screened 1019 patients who underwent PEA at Papworth Hospital. Of those, 42 patients fulfilled the criteria of having CTED	Definitely yes Reason: Objective measures were used.	Not applicable Reason: Outcome concerned quality of life	Not applicable Reason: The study design was prognostic	Not applicable Reason: The study design was prognostic	Definitely yes Reason: validated questionnaire data with ascertainment rules was used.	Definitely yes Reason: Follow up was up to 1 year after PEA. There was no loss to follow-up	Not applicable Reason: The study design was prognostic	**No concerns**
Erickson, 2019	Probably no Reason: This was a survey with an unknown	Probably yes Reason: the exposure was identified through self-	Not applicable Reason: Outcome concerned quality of life	Not applicable Reason: The study design was prognostic	Not applicable Reason: The study design was prognostic	Definitely yes Reason: validated questionnaire data with	Probably yes Reason: This was a a cross-sectional survey in		**Concerns. Unclear definitions of patient population, self-**

	response rate (but determined bu authors as 'less than ideal') that relied on patient self-report for index VTE identification and could only compare outcomes with aggregate findings drom a normal population. Recruitment went through a contract research agency	report (potential information bias)				ascertainment rules was used.	patients who self-reported VTE within the past 2 years before study enrollment. A total of 971 patients accessed and completed the online survey. Data cleaning resulted in 64 patients (6.5%) being removed from the final data.		**reported definitions of exposure. Recruitment and data collection for analysis were not carried out by the authors.**

Bijlage: Table ICHOM-studies that reported on the outcome quality of life

ICHOM ID	First author	Year	Title
5	Chen	2019	Long-Term Clinical Outcomes of Complicated Retrievable Inferior Vena Cava Filter for Deep Venous Thrombosis Patients: Safety and Effectiveness
7	Clay	2018	Cost-effectiveness of edoxaban compared to warfarin for the treatment and secondary prevention of venous thromboembolism in the UK
9	Guercini	2016	The management of patients with venous thromboembolism in Italy: insights from the PREFER in VTE registry
16	Kumar	2014	Health-Related Quality of Life in Children and Young Adults With Post-Thrombotic Syndrome: Results From a Cross-Sectional Study
25	Staniszewska	2020	The good, bad and the ugly of the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis trial from the viewpoint of clinicians
27	Svedman	2019	Deep venous thrombosis after Achilles tendon rupture is associated with poor patient-reported outcome
28	Wagenhäuser	2019	Clinical outcomes after direct and indirect surgical venous thrombectomy for inferior vena cava thrombosis
31	Vedantham	2017	Pharmacomechanical Catheter-Directed Thrombolysis for Deep- Vein Thrombosis
32	Schmitz	2019	Deep venous thrombosis and pulmonary embolism after anterior cruciate ligament reconstruction INCIDENCE, OUTCOME, AND RISK FACTORS
34	Kahn	2020	Quality of life after pharmacomechanical catheter-directed thrombolysis for proximal deep vein thrombosis
35	Wu	2018	The association between major complications of immobility during hospitalization and quality of life among bedridden patients: A 3 month prospective multi-center study
36	Haig	2016	Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial
40	Monreal	2019	Deep Vein Thrombosis in Europe—Health- Related Quality of Life and Mortality
42	Weinberg	2019	Relationships Between the Use of Pharmacomechanical Catheter-Directed Thrombolysis, Sonographic Findings, and Clinical Outcomes in Patients with Acute Proximal DVT: Results from the ATTRACT Multicenter Randomized Trial
47	Eirckson	2019	Understanding Factors Associated with Quality of Life in Patients with Venous Thromboembolism
56	Garcia	2020	Ultrasound-accelerated thrombolysis and venoplasty for the treatment of the postthrombotic syndrome: Results of the ACCESS PTS Study
59	Dumantepe	2019	Endophlebectomy of the common femoral vein and endovascular iliac vein recanalization for chronic iliofemoral venous occlusion

62	Bradbury	2019	A randomised controlled trial of extended anticoagulation treatment versus standard treatment for the prevention of recurrent venous thromboembolism (VTE) and post-thrombotic syndrome in patients being treated for a first episode of unprovoked VTE (the ExACT study)
64	Chuang	2019	Comparison of quality of life measurements: EQ-5D-5L versus disease/treatment-specific measures in pulmonary embolism and deep vein thrombosis
66	Sebastian	2020	Early clinical outcomes for treatment of post-thrombotic syndrome and common iliac vein compression with a hybrid oblique self-expanding nitinol stent – the TOPOS study
67	Razavi	2020	Correlation between Post-Procedure Residual Thrombus and Clinical Outcome in Deep Vein Thrombosis Patients Receiving Pharmacomechanical Thrombolysis in a Multicenter Randomized Trial
69	Engeseth	2019	Does the Villalta scale capture the essence of postthrombotic syndrome? A qualitative study of patient experience and expert opinion
70	Gombert	2018	Patency rate and quality of life after ultrasound-accelerated catheter-directed thrombolysis for deep vein thrombosis
71	Chuang	2018	Deep-vein thrombosis in Europe — Burden of illness in relationship to healthcare resource utilization and return to work
73	Strijkers	2015	Validation of the LET classification
74	Lutsey	2020	Long-Term Association of Venous Thromboembolism With Frailty, Physical Functioning, and Quality of Life: The Atherosclerosis Risk in Communities Study
76	Siddiqui	2020	Predictors of Poor Quality of Life after Primary Lower Limb Deep Venous Thrombosis: A Perspective from a Developing Nation
80	Utne	2018	Rivaroxaban versus warfarin for the prevention of post-thrombotic syndrome
82	Alibaz-Oner	2016	Post-thrombotic syndrome and venous disease-specific quality of life in patients with vascular Behçet's disease
90	Qian	2020	The perplexity of catheter-directed thrombolysis for deep venous thrombosis: the approaches play an important role
91	Ruihua	2017	Technique and Clinical Outcomes of Combined Stent Placement for Postthrombotic Chronic Total Occlusions of the Iliofemoral Veins
92	Ljungqvist	2018	Long-term quality of life and postthrombotic syndrome in women after an episode of venous thromboembolism
96	Jiang	2017	Mid-term outcome of endovascular treatment for acute lower extremity deep venous thrombosis
97	Wagenhäuser	2018	Open surgery for iliofemoral deep vein thrombosis with temporary arteriovenous fistula remains valuable
99	Hogg	2014	Validity of standard gamble estimated quality of life in acute venous thrombosis
104	Catarinella	2015	Quality-of-life in interventionally treated patients with post-thrombotic syndrome

107	Marvig	2015	Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants
108	Pesser	2020	Same Admission Hybrid Treatment of Primary Upper Extremity Deep Venous Thrombosis with Thrombolysis, Transaxillary Thoracic Outlet Decompression, and Immediate Endovascular Evaluation
110	Bi	2019	Long-term outcome and quality of life in patients with iliac vein compression syndrome after endovascular treatment
113	Engelberger	2017	Ultrasound-assisted versus conventional catheter-directed thrombolysis for acute iliofemoral deep vein thrombosis: 1-year follow-up data of a randomized-controlled trial
114	Dumantepe	2018	The effect of Angiojet rheolytic thrombectomy in the endovascular treatment of lower extremity deep venous thrombosis
115	Tichelaar	2016	A Retrospective Comparison of Ultrasound-Assisted Catheter-Directed Thrombolysis and Catheter-Directed Thrombolysis Alone for Treatment of Proximal Deep Vein Thrombosis
116	Nawasrah	2021	Incidence and severity of postthrombotic syndrome after iliofemoral thrombosis – results of the Iliaca-PTS – Registry
121	Lozano Sanchez	2013	Negative impact of deep venous thrombosis on chronic venous disease
123	Holmes	2014	Efficacy of a short course of complex lymphedema therapy or graduated compression stocking therapy in the treatment of post-thrombotic syndrome
124	Mol	2016	One versus two years of elastic compression stockings for prevention of post-thrombotic syndrome (OCTAVIA study): randomised controlled trial
128	Mean	2014	The VEINES-QOL/Sym questionnaire is a reliable and valid disease-specific quality of life measure for deep vein thrombosis in elderly patients
129	Broholm	2011	Postthrombotic syndrome and quality of life in patients with iliofemoral venous thrombosis treated with catheter-directed thrombolysis
135	Persson	2011	Deep venous thrombosis after surgery for achilles tendon rupture: a provoked transient event with minor long-term sequelae
136	Keita	2017	Assessment of quality of life, satisfaction with anticoagulation therapy, and adherence to treatment in patients receiving long-course vitamin K antagonists or direct oral anticoagulants for venous thromboembolism
141	Vogel	2012	Common femoral endovenectomy with iliocaval endoluminal recanalization improves symptoms and quality of life in patients with postthrombotic iliofemoral obstruction
142	Lee	2015	Role of coexisting contralateral primary venous disease in development of post-thrombotic syndrome following catheter-based treatment of iliofemoral deep venous thrombosis
145	Zhang	2013	A prospective randomized trial of catheter-directed thrombolysis with additional balloon dilatation for iliofemoral deep venous thrombosis: a single-center experience

150	Meng	2013	Stenting of iliac vein obstruction following catheter-directed thrombolysis in lower extremity deep vein thrombosis
152	Ast	2014	Clinical outcomes of patients with non-fatal VTE after toral knee arthroplasty
155	Lee	2021	Performance of two clinical scales to assess quality of life in patients with post-thrombotic syndrome
159	Ye	2016	Outcomes of stent placement for chronic occlusion of a filter-bearing inferior vena cava in patients with severe post-thrombotic syndrome
160	Enden	2013	Symptom burden and job absenteeism after treatment with additional catheter-direced thrombolysis for deep vein thrombosis
161	Roberts	2014	Post-thrombotic syndrome is an independent determinant of health-related quality of life following both first proximal and sital deep vein thrombosis
162	Kearon	2019	Pharmacomechanical catheter-directed thrombolysis in acute femoral-popliteal deep vein thrombosis: analysis from a stratified randomized trial
163	Yuan	2019	Diagnosis and treatment of acquired ateriovenous fistula after lower extremity deep vein thrombosis
166	Warner	2013	Functional outcomes following catheter-based iliac vein stent placement
170	Yu	2018	The midterm effect of iliac vein stenting following catheter-directed thrombolysis for the treatment of deep vein thrombosis
171	Sarici	2013	Our early experience with iliofemoral vein stenting in patients with post-thrombotic syndrome
172	Ye	2014	Technical details and clinical outcomes of transpopliteal venoous stent placement for postthrombotic chronic total occlusion of the iliofemoral vein
173	Comerota	2019	Endovascular thrombus reomval for acute iliofemoral deep vein thrombosis: analysis from a stratified multicenter randomized trial
8	Filipppo Corsi	2017	Life-threatening massive pulmonary embolism rescued by venoarterial- extracorporeal membrane oxygenation
33	Kline	2013	Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial
37	Rolving	2020	Effect of a Physiotherapist-Guided Home-Based Exercise Intervention on Physical Capacity and Patient-Reported Outcomes Among Patients With Acute Pulmonary Embolism A Randomized Clinical Trial
41	Kahn, S.	2017	Functional and Exercise Limitations After a First Episode of Pulmonary Embolism Results of the ELOPE Prospective Cohort Study
44	Keller, K.	2018	Quality of life and functional limitations after pulmonary embolism and its prognostic relevance
48	Tavoly, M.	2018	The impact of post-pulmonary embolism syndrome and its possible determinants
49	Stoller	2019	Clinical presentation and outcomes in elderly patients with symptomatic isolated subsegmental pulmonary embolism

50	Hoole	2020	Balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension: the UK experience
51	Kamenskaya	2020	Long-term health-related quality of life after surgery in patients with chronic thromboembolic pulmonary hypertension
52	Notten	2020	Prevalence of venous obstructions in (recurrent) venous thromboembolism: a case-control study
54	Taboada	2014	Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease
55	Cires-Drouet	2020	Safety of exercise therapy after acute pulmonary embolism
60	Chuang	2019	Health-related quality of life and mortality in patients with pulmonary embolism: a prospective cohort study in seven European countries
65	Jeong	2019	Relationship of Lower-extremity Deep Venous Thrombosis Density at CT Venography to Acute Pulmonary Embolism and the Risk of Postthrombotic Syndrome
68	Kamenskaya	2017	Factors affecting the quality of life before and after surgery in patients with chronic thromboembolic pulmonary hypertension
72	Darocha	2017	Improvement in Quality of Life and Hemodynamics in Chronic Thromboembolic Pulmonary Hypertension Treated With Balloon Pulmonary Angioplasty
75	Tavoly	2016	Health-related quality of life after pulmonary embolism: a cross-sectional study
77	Walen	2017	Safety, feasibility and patient reported outcome measures of outpatient treatment of pulmonary embolism
78	Knox	2019	Preservation of Cardiopulmonary Function in Patients Treated with Ultrasound-Accelerated Thrombolysis in the Setting of Submassive Pulmonary Embolism
79	Rao	2019	Ultrasound-assisted versus conventional catheter-directed thrombolysis for acute pulmonary embolism: A multicenter comparison of patient-centered outcomes
81	Ivarsson	2018	Health-related quality of life, treatment adherence and psychosocial support in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension
93	van Es	2013	Quality of life after pulmonary embolism as assessed with SF-36 and PEmb-QoL
98	Fukui	2016	Efficacy of cardiac rehabilitation after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension
102	Urushibara	2015	Effects of Surgical and Medical Treatment on Quality of Life for Patients With Chronic Thromboembolic Pulmonary Hypertension
103	Piazza	2020	One-Year Echocardiographic, Functional, and Quality of Life Outcomes After Ultrasound-Facilitated Catheter-Based Fibrinolysis for Pulmonary Embolism
105	Akaberi	2018	Determining the minimal clinically important difference for the PEmbQoL questionnaire, a measure of pulmonary embolism-specific quality of life

117	Harzheim	2013	Anxiety and depression disorders in patients with pulmonary arterial hypertension and chronic thromboemoblic pulmonary hypertension
118	Sertic	2020	Mid-term outcomes with the use of extracorporeal membrane oxygenation for cardiopulmonary failure secondary to massive pulmonary emoblism
122	Inagaki	2014	Home-based pulmonary rehabilitation in patients with inoperable or residual chronic thromboembolic pulmonary hypertension: A preliminary study
125	Kahn	2017	Quality of life, dyspnea, and functional exercise capacity following a first episode of pulmonary embolism: Results of the ELOPE Cohort Study
132	Barco	2021	Survival and quality of life after early discharge in low-risk pulmonary embolism
133	Stewart	2015	Contribution of fibrinolysis to the physical component summary of the SF-36 after acute submassive pulmonary embolism
138	Nagel	2012	Exercise training improves exercise capacity and quality of life in patients with inoperable or residual chronic thromboembolic pulmonary hypertension
139	Roman	2013	Health-related quality of life in a national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension
144	Marshall	2011	Surgical pumonary embolectomy: mid-terms outcomes
148	Kline	2016	Outpatient treatment of low-risk venous thromboembolism with monotherapy oral anticoagulation: patient quality of life outcomes and clinician acceptance
149	Tavoly	2015	Quality of life after pulmonary embolism: first cross-cultural evaluation of the pulmonary embolism quality-of-life (PEmb-QoL_ questionnaire in a Norwegian cohort
157	Valerio	2021	Quality of life three and twelve months after acute pulmonary embolism: analysis from a prospective multicenter cohort study
164	Berlier	2019	Real-life experience with Selexipag as an add-on therapy to oral combination therapy in patients with pulmonary arterial or distal chronic thromboembolic pulmonary hypertension: a retrospective analysis
165	Guth	2018	Exercise right heart catheterisation before and after pulmonary endarterectomy in patients with chronic thromboemoblic disease

Literature search strategy

ICHOM-search 08-03-2021

PubMed search 08-03-2021: **584 resultaten**, met gebruik van filters 'English language' en 'Publication in past 10 years'.

Daarnaast **420 non-PubMed resultaten:**

- Embase: 601 - 346 uniek
- Web of Science: 130 - 21 uniek
- Cochrane Library: 109 - 53 uniek (waaronder 29 clinicaltrialregister-items)

PubMed

((("venous thrombo-embolism"[tw] OR "venous thromboembolism"[tw] OR "deep venous thrombosis"[tw] OR **"DVT"[tw]** OR "Venous Thrombosis"[mesh] OR "venous thrombosis"[tw] OR "Pulmonary Embolism"[mesh] OR "pulmonary embolism"[tw]) AND ("Patient Reported Outcome Measures"[Mesh] **OR "PROMS"[tw]** OR "patient-reported"[tw] OR "patient reported"[tw] OR "patient-relevant"[tw] OR "patient relevant"[tw]) **NOT** (("Case Reports"[ptyp] OR "case report"[ti] OR "Clinical Trial Protocol"[ptyp] OR "protocol"[ti]) NOT ("Review"[ptyp] OR "review"[ti] OR "Clinical Study"[ptyp] OR "trial"[ti] OR "RCT"[ti])) **NOT** (("Child"[Mesh] OR "child"[ti] OR "children"[ti] OR "Infant"[Mesh] OR "infant"[ti] OR "infants"[ti] OR "infancy"[ti] OR "pediatr*"[ti] OR "paediatr*"[ti]) NOT ("Adult"[mesh] OR "adult"[ti] OR "adults"[ti] OR "elderly"[ti] OR "Adolescent"[Mesh] OR "adolescent"[ti] OR "adolescents"[ti] OR "adolescence"[ti])) **NOT** (("Animals"[mesh] OR "veterinary"[ti] OR "rabbit"[ti] OR "rabbits"[ti] OR "animal"[ti] OR "animals"[ti] OR "mouse"[ti] OR "mice"[ti] OR "rodent"[ti] OR "rodents"[ti] OR "rat"[ti] OR "rats"[ti] OR "pig"[ti] OR "pigs"[ti] OR "porcine"[ti] OR "horse"[ti] OR "horses"[ti] OR "equine"[ti] OR "cow"[ti] OR "cows"[ti] OR "bovine"[ti] OR "goat"[ti] OR "goats"[ti] OR "sheep"[ti] OR "ovine"[ti] OR "canine"[ti] OR "dog"[ti] OR "dogs"[ti] OR "feline"[ti] OR "cat"[ti] OR "cats"[ti]) NOT "Humans"[mesh])) **OR** (("venous thrombo-embolism"[ti] OR "venous thromboembolism"[ti] OR "deep venous thrombosis"[ti] OR **"DVT"[ti]** OR "Venous Thrombosis"[majr] OR "venous thrombosis"[ti] OR "Pulmonary Embolism"[majr] OR "pulmonary embolism"[ti]) AND ("Treatment Outcome"[majr] OR "**Treatment Outcome"[tiab] OR "Disease-Free Survival"[tiab] OR "Early Termination of Clinical Trials"[tiab] OR "Progression-Free Survival"[tiab] OR "Therapeutic Index"[tiab] OR "Treatment Failure"[tiab]** OR "Patient Reported Outcome Measures"[majr] **OR "PROMS"[tiab]** OR "patient-reported"[tiab] OR "patient reported"[tiab] OR "patient-relevant"[tiab] OR "patient relevant"[tiab] **OR "Quality of Life"[majr] OR "Quality of life"[tiab] OR "QoL"[tiab] OR "HRQoL"[tiab])** **NOT** (("Case Reports"[ptyp] OR "case report"[ti] OR "Clinical Trial Protocol"[ptyp] OR "protocol"[ti]) NOT ("Review"[ptyp] OR "review"[ti] OR "Clinical Study"[ptyp] OR "trial"[ti] OR "RCT"[ti])) **NOT** (("Child"[Mesh] OR "child"[ti] OR "children"[ti] OR "Infant"[Mesh] OR "infant"[ti] OR "infants"[ti] OR "infancy"[ti] OR "pediatr*"[ti] OR "paediatr*"[ti]) NOT ("Adult"[mesh] OR "adult"[ti] OR "adults"[ti] OR "elderly"[ti] OR "Adolescent"[Mesh] OR "adolescent"[ti] OR "adolescents"[ti] OR "adolescence"[ti])) **NOT** (("Animals"[mesh] OR "veterinary"[ti] OR "rabbit"[ti] OR "rabbits"[ti] OR "animal"[ti] OR "animals"[ti] OR "mouse"[ti] OR "mice"[ti] OR "rodent"[ti] OR "rodents"[ti] OR "rat"[ti] OR "rats"[ti] OR "pig"[ti] OR "pigs"[ti] OR "porcine"[ti] OR "horse"[ti] OR "horses"[ti] OR "equine"[ti] OR "cow"[ti] OR "cows"[ti] OR "bovine"[ti] OR "goat"[ti] OR "goats"[ti] OR "sheep"[ti] OR "ovine"[ti] OR "canine"[ti] OR "dog"[ti] OR "dogs"[ti] OR "feline"[ti] OR "cat"[ti] OR "cats"[ti]) NOT "Humans"[mesh]))**)**

Embase

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=main&MODE=ovid&D=oemezd

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Web of Science
http://isiknowledge.com/wos

((ab=("venous thromboembolism" OR "venous thrombo-embolism" OR "venous thromboembolism" OR "deep venous thrombosis" OR **"DVT"** OR "Vein Thrombosis" OR "venous thrombosis" OR "Lung Embolism" OR "pulmonary embolism") AND ti=("patient-reported outcome" OR **"PROMS"** OR "patient-reported" OR "patient reported" OR "patient-relevant" OR "patient relevant") **NOT** ti=(("Case Report" OR "case report" OR "Clinical Trial Protocol" OR "protocol") NOT ("Review" OR "review" OR "Clinical Study" OR "Clinical Trial" OR "trial" OR "RCT")) **NOT** ti=(("Child" OR "child" OR "children" OR "Infant" OR "infant" OR "infants" OR "infancy" OR "pediatr*" OR "paediatr*") NOT ("Adult" OR "adult" OR "adults" OR "elderly" OR "Adolescent" OR "adolescent" OR "adolescents" OR "adolescence")) **NOT**

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Module 3 Tromboseprofylaxe volwassenen met maligniteit

Autorisatie en geldigheid

Autorisatiedatum:	*pending*
Eerstvolgende beoordeling actualiteit	volgende cyclus binnen het cluster Antitrombotisch beleid
Geautoriseerd door:	*pending*
Belangrijkste wijzigingen t.o.v. vorige versie:	n.v.t., het betreft een nieuwe module
Herbevestiging:	n.v.t.
Regiehouder:	Nederlandse Internisten Vereniging

Uitgangsvraag

In hoeverre zouden poliklinische patiënten met een maligniteit tromboseprofylaxe moeten krijgen?

Introduction

Patients with cancer have an 8.5-fold increased risk of venous thromboembolism compared to the general population (Mulder, 2021). The 1-year cumulative incidence varies widely across different tumor types, ranging from 1% in patients with breast or prostate cancer to 10-20% in patients with gastric or pancreatic cancer. Cancer-associated thrombosis can lead to morbidity, decreased quality of life, interruption or delays in cancer treatment, and mortality, and is associated with increased healthcare costs. Ambulatory patients with cancer currently do not receive routine pharmacological thromboprophylaxis, but prevention of venous thromboembolism may prevent morbidity and mortality, particularly in high-risk patients. The term ambulatory is used for patients for whom care is usually organized and provided at the outpatient clinic, excluding those admitted to the hospital because of surgery or a medical illness, for whom the risk-benefit ratio of thromboprophylaxis is different. The current guideline does also not discuss prevention of catheter-associated thrombosis in patients with a central venous catheter, but focuses on thromboprophylaxis for prevention of any form of venous thromboembolism in a broad oncology population. Finally, recommendations do not pertain to patients with multiple myeloma, since these patients are already routinely treated with either aspirin or anticoagulation during cancer treatment based on hematological guidelines.

Search and select

A systematic review of the literature was performed to answer the following question: what are the (un)desirable effects of thromboprophylaxis with Direct Oral Anticoagulants (DOAC), Low-Molecular-Weight Heparin (LMWH) or fondaparinux in adult ambulatory patients with malignancy* in whom systemic anticancer treatment was initiated, compared to placebo or standard of care?

P	**(Patients)**	adult ambulatory patients with malignancy* initiating systemic anticancer treatment
I	**(Intervention)**	thromboprophylaxis (DOAC, LMWH, or fondaparinux)
C	**(Comparison)**	placebo, standard of care
O	**(Outcomes)**	net clinical benefit, venous thromboembolism, major bleeding, mortality, clinically relevant non-major bleeding

(CRNMB), arterial thromboembolism (ATE), quality of life, discontinuation of oncological treatment/complementary treatments, quality of dying and death

*Excluding patients with multiple myeloma, since these patients are already routinely treated with either aspirin or anticoagulation during cancer treatment based on hematological guidelines.

Relevant outcome measures

The guideline development group considered net clinical benefit and mortality as critical outcome measures for decision making; any thromboembolism and CRNMB, quality of life, discontinuation of oncological treatment/complementary treatments, and quality of dying and death as an important outcome measure for decision making.

The working group defined the outcomes as follows:

- VTE: incidental or symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE)
- Net clinical benefit: composite of non-fatal VTE, non-fatal major bleeding and mortality
- Major bleeding: fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin levels of 1.24 mmol/L (20 g/L or greater) or more, or leading to a transfusion of 2 U or more of whole blood or red cells, as defined by International Society on Thrombosis and Haemostasis;

A priori, the working group did not define the other outcome measures listed above but used the definitions used in the studies.

The working group defined the following as a minimal clinically (patient) important difference:

- Net clinical benefit, VTE, major bleeding, mortality, CRNMB, ATE: risk difference of 3%*
- For all other outcome measures, the default thresholds proposed by the international GRADE working group were used as a threshold for clinically relevant differences: a 25% difference in relative risk (RR) for dichotomous outcomes (RR <0.8 or RR >1.25), and 0.5 standard deviations (SD) for continuous outcomes.

**Based on the differences applied in the guidelines on thromboprophylaxis in patients with COVID-19. This working group derived the minimal clinically (patient) important differences from the ACCP (2012).*

Search and select (Methods)

First search

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until July 4th, 2023. The systematic literature search resulted in 104 hits. Studies were selected based on the following criteria: (systematic reviews of) ≥ Phase III RCTs which compared the efficacy of thromboprophylaxis (DOAC, LMWH, fondaparinux) with placebo or no thromboprophylaxis in adult ambulatory patients with malignancy, initiating systemic anticancer treatment. 22 studies were initially selected based on title and abstract screening. After reading the full text, 21 studies were excluded (see the table with

reasons for exclusion under the tab Methods), and one study was included (Cochrane Review of Rutjes, 2020).

Second search

An additional search was performed to complement the evidence in the Cochrane Review of Rutjes (2020). It was decided to omit the term 'ambulatory', in order to be sure that all relevant studies were found. The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until October 12th, 2023. The systematic literature search resulted in 819 hits. Studies were selected based on the following criteria: (systematic reviews of) ≥ Phase III RCTs which compared the efficacy of thromboprophylaxis (DOAC, LMWH, fondaparinux) with placebo or no thromboprophylaxis in adult patients with malignancy, initiating systemic anticancer treatment. One study was initially selected based on title and abstract screening. After reading the full text, this study was included (Alexander, 2023).

The detailed search strategies are shown under the tab Methods.

Results

Two studies were included in the analysis of the literature (Rutjes, 2020 and Alexander, 2023). Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Rutjes (2020) performed a systematic review to evaluate the effect of primary thromboprophylaxis in adult ambulatory patients with malignancy initiating chemotherapy. Several databases were searched up to August 2020, including The Cochrane Vascular Specialized Register, Cochrane Central Register of Controlled Trials, Medline, Embase, CINAHL EBSCO, and AMED Ovid. They included studies including ambulatory patients (outpatient) (children and adults) with either solid or hematological cancer at any stage. In total, 32 studies (N=15,678) were included. Of those studies, eight (≥ Phase III) studies* reported data on the effect of thromboprophylaxis with DOAC, LMWH, or fondaparinux in adult patients, compared to placebo or standard of care (no thromboprophylaxis). Quality of the studies was assessed using the Cochrane's risk of bias tool. Table 1 lists more details on the eight studies that were included in our literature analysis. Most studies were (partly) funded by pharmaceutical companies. For the studies of Agnelli (2009) and Khorana (2019), it was reported that the sponsoring party had an active role in writing and/or editing the manuscript and/or in interpreting the data.

In general, the studies included patients who are at (higher) risk of developing thrombosis. Therefore, the included study population will not reflect the full spectrum of the target population, namely patients with a malignancy initiating systemic treatment.

*Reasons for exclusion of studies are described in the table under the tab Methods.

Alexander (2023) performed an open-label RCT (TARGET-TP) to evaluate the effect of thromboprophylaxis with enoxaparin in adult patients with lung or gastrointestinal cancer, receiving anti-cancer therapy with or without radiotherapy/immunotherapy. Based on fibrinogen and D-dimer levels, 200 patients (61%) were classified as being at high risk of venous thromboembolism. These 200 high-risk patients were randomized to receive either enoxaparin (40 mg, subcutaneously, once daily for ≤ 90 days, N=100) or no thromboprophylaxis (control group, N=100). Median age (range) was 67 (30-87) years in the enoxaparin group and 66 (31-85) in the control group. Of the patients in the enoxaparin group, 62 (62%) were male, compared to 55 (55%) in the control group. In the enoxaparin

group were 52 (52%) and 5 (5%) patients with respectively metastatic disease and prior thromboembolism, compared to 44 (44%) and 7 (7%) patients in the control group. Primary follow-up was 180±30 days.

Table 1: Details of studies that are included in the literature analysis on the effect of thromboprophylaxis in ambulatory patients with cancer initiating chemotherapy, adapted from Rutjes (2020).

Author, year	Participants (N)	Disease characteristics	Intervention	Comparison	Follow-up (median (IQR))
Agnelli, 2009 (PROTECHT-trial)	I: 779, C: 387	Metastatic or locally advanced lung, gastrointestinal, pancreatic, breast, ovarian, or head and neck cancer	Nadroparin 3800 IU SC, once daily for max. 120±10 days /duration of chemotherapy, median duration: NR	Placebo	I: 111 days (NR), C: 113 (NR) days
Altinbas, 2004	I: 42, C: 42	Small-cell lung carcinoma, ECOG performance <3 and normal haematological, renal, and hepatic function tests	Dalteparin 5000 IU SC, once daily, median (IQR) duration: 18 weeks (NR)	No dalteparin	10 (2-33 (range)) months
Sideras, 2006*	first part: n=50, I: 24, C:26 second part: n=88, I: 44, C: 44	Advanced breast cancer, failed first-line chemotherapy; advanced prostate cancer, failed primary hormonal therapy; advanced lung cancer; or advanced colorectal cancer	Dalteparin 5000 IU SC, for 18 weeks or until disease progression, median duration: NR	First part from dec 1998 to feb 2020 placebo, second part from feb 2020 to June 2021 standard care alone	NR, 18 months was planned
Kakkar, 2004 (FAMOUS-trial)	I: 196, C: 189	Advanced stage III/IV cancer of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary, or uterus.	Dalteparin 5000 IU SC, once daily for 1 year or until death, median duration: NR	Placebo	I: 10 (NR) months, C: 9 (NR) months
Perry, 2010 (PRODIGE trial)	I: 98, C: 88	Grade 3 or grade 4 Glioma	Dalteparin 5000 IU SC, once daily, median (IQR) duration: 183 (NR) days.	Placebo Median (IQR) duration: 157 (NR) days	NR, 12 months was planned

Macbeth, 2016 (FRAGMATIC-trial)	I: 102, C: 1101	Primary bronchial carcinoma of any stage and histology	Dalteparin 5000 IU SC, once daily for 24 weeks (median duration: NR, reported was that 180 (18.4%) patients received full number of syringes)	Standard care	23.1 (3.6-31.2) months
Khorana, 2019 (CASSINI-trial)	I: 436, C: 421	High-risk ambulatory patients with solid cancer or lymphoma who had a Khorana score of ≥ 2, had a plan to start a new systemic regimen within 1 week before or after initiating the trial regimen and had no DVT on baseline screening ultrasonography.	Rivaroxaban 10 mg, once daily up to 180 days, mean (range) duration: 4.3 (NR) months	Placebo	NR
Carrier, 2019 (AVERT- trial)	I: 291, C: 283	Patients with a newly diagnosed cancer site or progression of the malignant disease after complete or partial remission who were initiating a new course of chemotherapy with a minimum intent of 3 months' therapy and who had a Khorana score of ≥ 2.	Apixaban 2.5 mg, twice daily for 6 months, median (IQR) duration:157 (78-168) days	Placebo Median (IQR) duration:155 (83-168) days	183 (NR) days

C: control, I: intervention, NR: not reported, ECOG: Eastern Cooperative Oncology Group
***The study was modified because of concerns that the low accrual rate was related to the requirements for placebo injections (first phase). The saline placebo injections were eliminated, then, unblinded LMWH was compared with standard clinical care (second phase).**

5

Results

Net clinical benefit

Net clinical benefit was defined as a composite outcome of non-fatal VTE, non-fatal major bleeding and mortality. We used non-fatal VTE and non-fatal major bleeding in calculating net clinical benefit to prevent double counting of fatal events. In randomized controlled trials evaluating thromboprophylaxis, major bleeding events are usually assessed during the study treatment period, while VTE is assessed during the whole follow-up period. This should have prevented double counting of patients who potentially developed a non-fatal VTE and subsequently developed a non-fatal major bleeding after initiating anticoagulation. Only studies that reported on non-fatal VTE, non-fatal major bleeding, and mortality are included in the analysis on the outcome measure net clinical benefit.

We first describe the results on the outcomes VTE, major bleeding, and mortality separately and thereafter report the results on the outcome measure net clinical benefit.

Venous thromboembolism

Rutjes (2020) defined the outcome VTE as symptomatic and incidental VTE (DVT and PE).

DOACs

Two studies reported on the outcome VTE (Carrier, 2019 and Khorana, 2019). In the trial evaluating apixaban (Carrier, 2019), the outcome was symptomatic or incidentally detected VTE (DVT and PE). In the trial evaluating rivaroxaban (Khorana, 2019), the outcome was symptomatic or incidentally detected VTE (DVT and PE), also including DVT detected by serial screening ultrasonography, which was performed at weeks 8, 16, and 26.

In the apixaban group, 12/288 (4.2%) patients developed VTE compared to 28/275 (10.2%) patients in the placebo group (Carrier, 2019). This corresponds to a risk ratio (RR, 95%CI) of 0.41 (0.21 to 0.79). Risk difference (RD, 95%CI) was -0.06 (-0.10 to -0.02), which was in favour of the apixaban group and was considered clinically relevant. Corresponding NNT is -17 (-10 to -50).

In the rivaroxaban group, 25/420 (6.0%) patients developed VTE compared to 37/421 (8.8%) patients in the placebo group (Khorana, 2019). This corresponds to a RR (95%CI) of 0.68 (0.42 to 1.10). RD (95%CI) was -0.03 (-0.06 to 0.01), which was in favour of the rivaroxaban group and considered to be (borderline) clinically relevant. Corresponding NNT (95%CI) is -33 (-17 to 100).

LMWH

Three studies reported on the outcome VTE (Agnelli, 2009; Alexander, 2023 and Macbeth, 2016). Other studies reported on symptomatic VTE (Altinbas, 2004; Kakkar, 2004; Sideras, 2006 and Perry, 2010). Despite this, results of those seven studies were pooled.

In the LMWH-group 105/2369 (4.4%) patients developed VTE, compared to 169/1965 (8.6%) patients in the control group (Figure 1). This corresponds to a RR (95%CI) of 0.57 (0.45 to 0.72). RD (95%CI) was -0.03 (-0.05 to -0.01), which was in favour of the LMWH-group and considered to be clinically relevant (borderline). Corresponding NNT (95%CI) is -33 (-20 to -100).

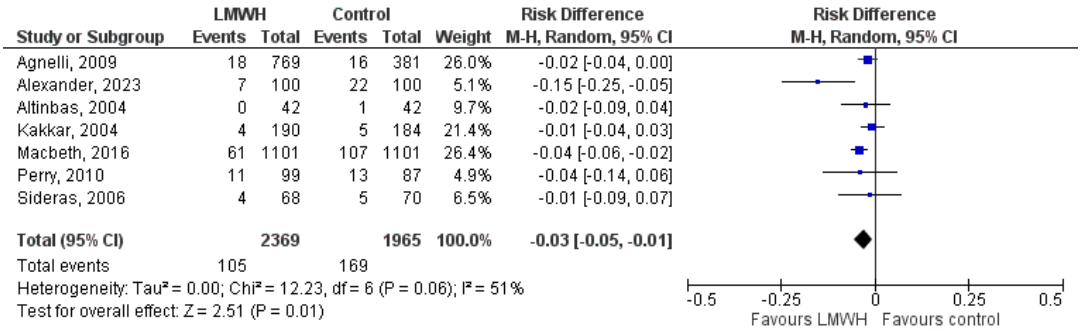


Figure 3: The effect of LMWH on the outcome VTE in adult patients with malignancy initiating chemotherapy. Based on Rutjes (2020) and Alexander (2023).

Fondaparinux

None of the included studies used fondaparinux as thromboprophylaxis in patients with malignancy initiating chemotherapy.

Major bleeding

Rutjes (2020) defined the outcome major bleeding as an overt bleeding associated with a decrease in hemoglobin of 2 g/dL or more or leading to a transfusion of two or more units of packed red blood cells or whole blood; bleeding that occurred at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or bleeding contributing to death. This definition is identical to the definition of major bleeding as per the International Society on Thrombosis and Haemostasis.

DOACs

Two studies reported on the outcome major bleeding (Carrier, 2019 and Khorana, 2019). In the apixaban group 10/288 (3.5%) patients had a major bleeding while receiving study drug, compared to 5/275 (1.8%) patients in the placebo group (Carrier, 2019). This corresponds to a RR (95%CI) of 1.91 (0.66 to 5.52). RD (95%CI) was 0.02 (-0.01 to 0.04), which was in favour of the placebo group and not considered to be clinically relevant. Corresponding NNH (95%CI) is 50 (-100 to 25).

In the rivaroxaban-group 8/405 (2%) patients had a major bleeding while receiving study drug, compared to 4/404 (1%) patients in the placebo group (Khorana, 2019). This corresponds to a RR (95%CI) of 2.00 (0.61 to 6.57). RD (95%CI) was 0.01 (-0.01 to 0.03), which was in favour of the placebo group and not considered to be clinically relevant. Corresponding NNH (95%CI) is 100 (-100 to 33).

LMWH

Six studies reported on the outcome major bleeding (Alexander, 2023; Agnelli, 2009; Kakkar, 2004; Macbeth, 2016; Perry, 2010 and Sideras, 2006).

In the LMWH-group 26/2327 (1.1%) patients had a major bleeding while receiving study drug, compared to 16/1923 (0.8%) patients in the control group (Figure 2). This corresponds to a RR (95%CI) of 1.35 (0.67 to 2.70). RD (95%CI) was 0.01 (0.00 to 0.01), which was in favour of the control group and not considered to be clinically relevant. Corresponding NNH (95%CI) is 100 (0 to 100).

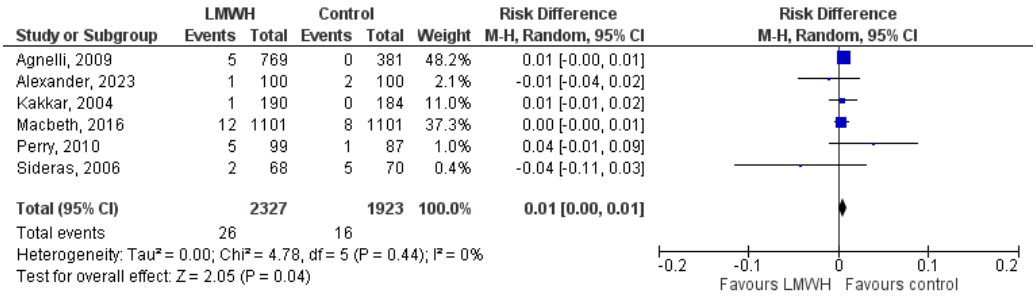


Figure 2: The effect of LMWH on the outcome major bleeding in adult patients with malignancy initiating chemotherapy. Based on Rutjes (2020) and Alexander (2023).

Fondaparinux

None of the included studies used fondaparinux as thromboprophylaxis treatment in patients with malignancy initiating chemotherapy.

Mortality

Rutjes (2020) defined the outcome mortality as one year overall mortality and therefore we derived the data on all-cause mortality from the individual studies. Macbeth (2016), Carrier (2019) and Khorana (2019) defined mortality as all-cause mortality within the study period.

DOACs

Two studies reported on the outcome mortality (Carrier, 2019 and Khorana, 2019). In the apixaban group 35/288 (12.2%) patients died, compared to 27/275 (9.8%) patients in the placebo group (Carrier, 2019). This corresponds to a RR (95%CI) of 1.24 (0.77 to 1.99). RD (95%CI) was 0.02 (-0.03 to 0.07), which was in favour of the placebo group and not considered to be clinically relevant. Corresponding NNT (95%CI) is 50 (-33.3 to 14.3).
In the rivaroxaban group 84/420 (20%) patients died, compared to 100/421 (23.8%) patients in the placebo group (Khorana, 2019). This corresponds to a RR (95%CI) of 0.84 (0.65 to 1.09). RD (95%CI) was -0.04 (-0.09 to 0.02), which was in favour of the rivaroxaban group and not considered to be clinically relevant. Corresponding NNT (95%CI) is -25 (-11 to 50).

LMWH

Seven studies reported on the outcome mortality (Agnelli, 2009; Alexander, 2023; Altinbas, 2004; Kakkar, 2004; Macbeth, 2016; Perry, 2010 and Sideras, 2006). In the LMWH-group 1552/2369 (65.5.%) patients died compared to 1414/1965 (72.0%) patients in the control group (Figure 3). This corresponds to a RR (95%CI) of 0.97 (0.87 to 1.08). RD (95%CI) was -0.03 (-0.08 to 0.03), which was in favour of the LMWH-group and considered to be (borderline) clinically relevant. Corresponding NNT (95%CI) was -33 (-12.5 to 33).

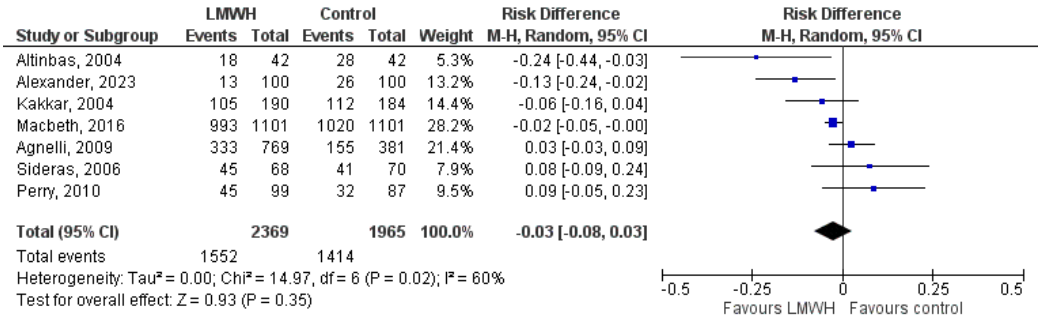


Figure 3: The effect of LMWH on the outcome all-cause mortality in adult patients with malignancy initiating chemotherapy. Based on Rutjes (2020) and Alexander (2023).

Fondaparinux

None of the included studies used fondaparinux as thromboprophylaxis in patients with malignancy initiating chemotherapy.

Net clinical benefit

DOACs

Carrier (2019) and Khorana (2019) reported on the outcomes non-fatal VTE, non-fatal major bleeding and all-cause mortality, from which the net clinical benefit could be calculated. Results are described in Table 2. Net clinical benefit calculated using results of Khorana (2019) was considered clinically relevant, which was not the case for net clinical benefit calculated based on Carrier (2019).

LMWH

Agnelli (2009) and Sideras (2006) reported on the outcomes non-fatal VTE, non-fatal major bleeding and one-year mortality, from which the net clinical benefit could be calculated. Results are described in Table 2. The calculated net clinical benefit was not considered to be clinically relevant.

Table 2: Net clinical benefit of thromboprophylaxis in adult patients with malignancy initiating chemotherapy (Agnelli, 2009; Sideras, 2006; Carrier, 2019 and Khorana, 2019).

	Non-fatal VTE (n/N)	Non-fatal major bleeding (n/N)	Mortality (n/N)	Net clinical benefit (n/N)
LMWH				
Agnelli (2009)	I: 18/769 C: 16/381	I: 4/769 C: 0/381	I: 333/769 C: 155/381	RD (95%CI): 0.01 (-0.05 to 0.07)
Sideras (2006)	I: 4/68 C: 5/70	I: 1/68 C: 4/70	I: 45/68 C: 41/70	RD (95%CI): 0.02 (-0.13 to 0.17)
DOAC				
Carrier (2019)	I: 12/288 C: 28/275	I: 10/288 C: 5/275	I: 35/288 C: 27/275	RD (95%CI): -0.02 (-0.09 to 0.05)
Khorana (2019)	I: 24/420 C: 34/421	I: 7/405 C: 4/404	I: 84/420 C: 100/421	RD (95%CI): -0.05 (-0.12 to 0.01)

DOAC: direct oral anticoagulants; LMWH: low molecular weight heparin, RD: Risk Difference, VTE: venous thromboembolism, I:intervention , C:comparison, CI: confidence interval.

Clinically relevant non-major bleeding

Rutjes (2020) reported on the outcome clinically relevant bleeding, which was defined as major and clinically relevant non-major bleeding. Therefore, data on CRNMB is derived from the individual studies.

DOACs

Two studies reported on the outcome CRNMB, which was defined according to ISTH criteria as bleeding not meeting the definition of major bleeding, but leading to an intervention, hospitalization, increased level of care, or face to face evaluation (Carrier, 2019 and Khorana, 2019). In the apixaban group 21/288 (7.3%) patients developed CRNMB while receiving study drug, compared to 15/275 (5.5%) patients in the placebo group (Carrier, 2019). This corresponds to a hazard ratio (HR, 95%CI) 1.28 (0.89 to 1.84). RD (95%CI) was

0.02 (-0.02 to 0.06), which was in favour of the placebo group and not considered to be clinically relevant. Corresponding NNH (95%CI) is 50 (-50 to 17).
In the rivaroxaban-group 11/405 (2.7%) patients developed CRNMB while receiving study drug, compared to 8/404 (2%) patients in the placebo group (Khorana, 2019). This corresponds to a hazard ratio (HR, 95%CI) 1.34 (0.54 to 3.32). RD (95%CI) was 0.01 (-0.01 to 0.03), which was in favour of the placebo group and not considered to be clinically relevant. Corresponding NNH (95%CI) is 100 (-100 to 33).

LMWH

One study reported on the outcome CRNMB, which was defined as bleeding not meeting criteria for major bleeding but that would be considered relevant and not trivial by a patient (Alexander, 2023). In the LMWH-group, 16/100 (16%) patients developed CRNMB while receiving study drug, compared to 9/100 (9%) patients in the control group. Adjusted HR (95%CI) was 2.63 (0.23 to 29.71). RD (95%CI) was 0.07 (-0.02 to 0.16), which was in favour of the control group and considered to be clinically relevant. Corresponding NNH (95%CI) was 14 (-50 to 6).

Fondaparinux

None of the included studies used fondaparinux as thromboprophylaxis in patients with malignancy initiating chemotherapy.

Arterial thromboembolism

Rutjes (2020) reported on the outcome ATE, which was defined as symptomatic ATE. However, for the study of Carrier (2019) data on ATE were not available in Rutjes (2020). The working group knew the systematic review and meta-analysis of Xu (2023) in which this data was reported. Therefore, for the study of Carrier (2019) data on the outcome ATE are deduced from Xu (2023). Xu (2023) did not have complementary data on the outcome ATE for the comparisons on LMWH.

DOACs

Two studies reported on the outcome ATE (Carrier, 2019 and Khorana, 2019).
In the apixaban group 1/288 (0.3%) patients developed ATE, compared to 0/275 (0%) patients in the placebo group. This corresponds to a RR (95%CI) of 2.87 (0.12 to 70.03). RD (95%CI) was 0.00 (-0.01 to 0.01), which was in favour of the placebo group and not considered to be clinically relevant. Corresponding NNT (95%CI) was 0 (-100 to 100).
In the rivaroxaban-group 4/420 (1%) patients developed ATE, compared to 7/421 (1.7%) patients in the placebo group. This corresponds to a RR (95%CI) of 0.57 (0.17 to 1.94). RD (95%CI) was -0.01 (-0.02 to 0.01), which was in favour of the rivaroxaban group and not considered to be clinically relevant. Corresponding NNT (95%CI) was -100 (-50 to 100).

LMWH

Three studies reported on the outcome ATE, which was not further specified in Rutjes (2020) (Agnelli, 2009; Alexander, 2023 and Macbeth, 2016). In the LMWH-group, 28/1970 (1.4%) patients developed ATE, compared to 31/1582 (2.0%) patients in the control group (Figure 4). This corresponds to a RR (95%CI) of 0.84 (0.51 to 1.40). RD (95%CI) was -0.00 (-0.01 to 0.00), which was in favour of the LMWH-group and not considered to be clinically relevant. Corresponding NNT (95%CI) was 0 (-100 to 0).

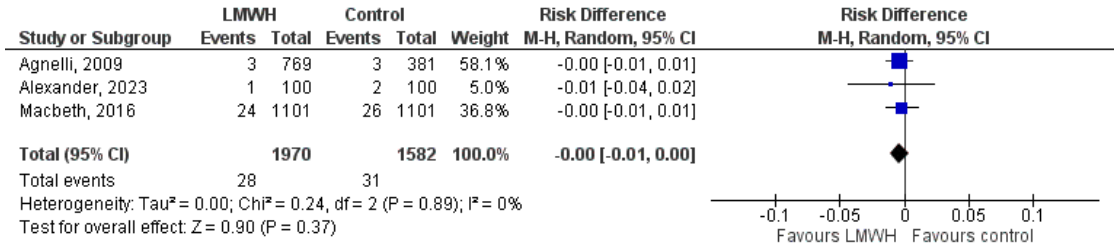


Figure 4: The effect of LMWH on the outcome arterial thromboembolic events in adult patients with malignancy initiating chemotherapy. Based on Rutjes (2020) and Alexander (2023).

Fondaparinux

None of the included studies used fondaparinux as thromboprophylaxis in patients with malignancy initiating chemotherapy.

Quality of life

DOACs

None of the included studies on the effect of thromboprophylaxis with DOACs in patients with malignancy initiating chemotherapy reported on the outcome QoL.

LMWH

Two studies reported on the outcome QoL (Macbeth, 2016 and Sideras, 2006). Sideras (2006) measured QoL using the single-item tool Uniscale and a 5-item series of self-assessment measures supplemented by a 13-item symptom distress scale. In the LMWH-group, 37/68 (54.4%) patients had a decrease of ≥ 10 points on the 100-point scale Uniscale, compared to 36/70 (51.4%) patients in the control group. This corresponds to a RR (95%CI) of 1.06 (0.77 to 1.45), which was in favour of the control group. This difference was not considered clinically relevant.

Macbeth (2016) used the Hospital Anxiety and Depression Score and the EuroQol 5 Dimensions (EQ-5D) to assess QoL. At six months follow-up, the mean EQ-5D score (±SD) was 69.95±26.65 in the LMWH-group (N=486), compared to 69.84±24.89 in the control group (N=454). This corresponds to a mean difference (95%CI) of 0.11 (–3.18 to 3.40), which was in favour of the LMWH-group. This difference was not considered clinically relevant. At 12 months follow-up, the mean EQ-5D score (±SD) was 68.08±25.92 in the LMWH-group (N=221), compared to 68.42±26.95 in the control group (N=224). This corresponds to a mean difference (95%CI) of –0.34 (–5.25 to 4.57), which is in favour of the control group. This difference was not considered clinically relevant.

Fondaparinux

None of the included studies used fondaparinux as thromboprophylaxis in patients with malignancy initiating chemotherapy.

Discontinuation of oncological treatment/complementary treatments and quality of dying and death

None of the included studies reported on the outcome measures discontinuation of oncological treatment/complementary treatments and quality of dying and death.

Level of evidence of the literature

Fondaparinux

None of the included studies used fondaparinux as thromboprophylaxis in patients with malignancy initiating chemotherapy. Therefore, no conclusion can be drawn on the effect of thromboprophylaxis with fondaparinux on all outcome measures in adult ambulatory

patients with malignancy, initiating chemotherapy compared with placebo or no thromboprophylaxis.

General remarks on industry sponsorship

Most studies were (partly) funded by pharmaceutical companies. For the studies of Agnelli (2009) and Khorana (2019) it was reported that the sponsoring party had an active role (e.g. interpretation of the data, writing and/or editing the manuscript). However, the level of evidence was not further downgraded because it is unlikely to have had an influence on the results because of the a priori defined outcomes, double blind design, and adjudication of outcome events.

Net clinical benefit

DOACs

Evidence regarding the outcome measure net clinical benefit comes from RCTs and therefore the level of evidence started as high. The level of evidence was downgraded to low. There was risk of bias (attrition bias, sampling bias, serial screening for DVT; downgraded one level). Furthermore, the 95%CI of the effect estimate crossed one of the thresholds for clinical relevance (imprecision, downgraded one level).

LMWH

Evidence regarding the outcome measure net clinical benefit comes from RCTs and therefore the level of evidence started as high. The level of evidence was downgraded to very low. There was risk of bias (open label trial, attrition bias, selection bias; downgraded one level). Furthermore, the 95%CI of the effect estimate crossed the thresholds for clinical relevance (imprecision, downgraded two levels).

Venous thromboembolism

DOACs

Evidence regarding the outcome VTE comes from RCTs and therefore the level of evidence started as high. The level of evidence was downgraded to low. There was risk of bias (attrition bias, sampling bias, serial screening on DVT; downgraded one level). Furthermore, the 95%CI of the effect estimate crossed one of the thresholds for clinical relevance (imprecision, downgraded one level).

LMWH

Evidence regarding the outcome VTE comes from RCTs and therefore the level of evidence started as high. The level of evidence was downgraded to low. There was risk of bias (e.g. attrition bias and open-label trials, downgraded one level). Furthermore, the 95%CI of the effect estimate crossed one of the thresholds for clinical relevance (imprecision, downgraded one level).

Major bleeding

DOACs

Evidence regarding the outcome major bleeding comes from RCTs and therefore the level of evidence started as high. The level of evidence was downgraded to low. There was risk of bias (attrition bias, sampling bias; downgraded one level). Furthermore, the 95%CI of the effect estimate crossed one of the thresholds for clinical relevance (imprecision, downgraded one level).

LMWH

Evidence regarding the outcome major bleeding comes from RCTs and therefore the level of evidence started as high. The level of evidence was downgraded to very low. There was high risk of bias (attrition bias, open label trials, downgraded one level). The results were inconsistent (inconsistency, downgraded one level) and the number of events was low (imprecision, downgraded one level).

Mortality

DOACs

Evidence regarding the outcome mortality comes from RCTs and therefore the level of evidence started as high. The level of evidence was downgraded to very low. There was risk of bias (attrition bias, sampling bias; downgraded one level). Furthermore, the 95%CI of the effect estimate crossed the thresholds for clinical relevance (imprecision, downgraded two levels).

LMWH

Evidence regarding the outcome mortality comes from RCTs and therefore the level of evidence started as high. The level of evidence was downgraded to very low. There was risk of bias (e.g. attrition bias, downgraded one level). Results were inconsistent (inconsistency, downgraded one level) and 95%CI of the effect estimate crossed the thresholds for clinical relevance (imprecision, downgraded one level). It was decided to downgrade one level for imprecision, due to the fact that part of the imprecision might be attributable to the inconsistent results.

Clinically relevant non-major bleeding

DOACs

Evidence regarding the outcome mortality comes from RCTs and therefore the level of evidence started as high. The level of evidence was downgraded to low. There was risk of bias (attrition bias, sampling bias; downgraded one level). Furthermore, the number of events was low (imprecision, downgraded one level).

LMWH

Evidence regarding the outcome CRNMB comes from a RCT and therefore the level of evidence started as high. The level of evidence was downgraded to very low. There was risk of bias (unclear follow-up and open label trial, downgraded one level). Furthermore, the 95%CI of the effect estimate crossed one of the thresholds for clinical relevance and the number of events was low (imprecision, downgraded two levels).

Arterial thromboembolism

DOACs

Evidence regarding the outcome ATE comes from RCTs and therefore the level of evidence started as high. The level of evidence was downgraded to very low. There was risk of bias (attrition bias, sampling bias; downgraded one level). Furthermore, the number of events was very low (serious imprecision, downgraded two levels).

LMWH

Evidence regarding the outcome ATE comes from RCTs and therefore the level of evidence started as high. The level of evidence was downgraded to very low. There was risk of bias (e.g. attrition bias, open label trials, downgraded one level). Furthermore, the number of events was very low (imprecision, downgraded two levels).

Quality of life

DOACs

None of the included studies on the effect of thromboprophylaxis with DOACs in patients with malignancy receiving chemotherapy reported on the outcome measure quality of life.

Therefore, no conclusion can be drawn on the effect of thromboprophylaxis with DOACs on the outcome measure quality of life in adult ambulatory patients with malignancy, receiving chemotherapy.

LMWH

Evidence regarding the outcome measure QoL comes from RCTs and therefore the level of evidence started as high. The level of evidence was downgraded to very low. There was risk of bias (e.g. open label trials, downgraded two levels). Furthermore the 95%CI of the effect estimate crossed the thresholds for clinical relevance (imprecision, downgraded two levels).

Discontinuation of oncological treatment/complementary treatments and quality of dying and death in the palliative care setting

None of the included studies reported on the outcome measures discontinuation of oncological treatment/complementary treatments and quality of dying and death.

Therefore, no conclusion can be drawn on the effect of thromboprophylaxis with DOAC, LMWH, or fondaparinux on the outcome measures discontinuation of oncological treatment/complementary treatments and quality of dying and death in adult ambulatory patients with malignancy, initiating chemotherapy compared to placebo or no thromboprophylaxis.

Conclusions

General remark

The studies included predominantly patients who are at (higher) risk of developing thrombosis. Therefore, the results might not be applicable to *all* patients with malignancy who are initiating systemic treatment.

All outcome measures – fondaparinux

No GRADE	None of the included studies used fondaparinux as thromboprophylaxis in patients with malignancy receiving chemotherapy. Therefore, no conclusion can be drawn on the effect of thromboprophylaxis with fondaparinux on all outcome measures in adult ambulatory patients with malignancy initiating chemotherapy. *Sources: none*

Net clinical benefit

DOAC

Low GRADE	In adult ambulatory patients with malignancy initiating chemotherapy and an intermediate to high risk Khorana-score and no risk factors for bleeding, thromboprophylaxis with DOACs may result in a net clinical benefit which is clinically relevant, compared to placebo. *Sources: Carrier, 2019 and Khorana, 2019*

LMWH

Very low GRADE	The evidence is very uncertain about the effect of thromboprophylaxis with LMWH on the outcome net clinical benefit when compared with placebo or standard of care in adult ambulatory patients with malignancy initiating chemotherapy.

	Sources: Agnelli, 2009 and Sideras, 2006

Mortality

DOAC

Very low GRADE	The evidence is very uncertain about the effect of thromboprophylaxis with DOACs on the outcome mortality when compared with placebo in adult ambulatory patients with malignancy initiating chemotherapy and an intermediate to high risk Khorana-score. *Sources: Carrier, 2019 and Khorana, 2019*

LMWH

Very low GRADE	The evidence is very uncertain about the effect of thromboprophylaxis with LMWHs on the outcome mortality when compared with placebo or standard of care in adult ambulatory patients with malignancy initiating chemotherapy. *Sources: Agnelli, 2009; Alexander, 2023; Altinbas, 2004; Kakkar, 2004; Macbeth, 2016; Perry, 2010 and Sideras, 2006*

Venous thromboembolism

DOAC

Low GRADE	In adult ambulatory patients with malignancy initiating chemotherapy and an intermediate to high risk Khorana-score and no risk factors for bleeding, thromboprophylaxis with DOACs may result in a reduction in number of patients with a VTE, compared to placebo. *Sources: Carrier, 2019 and Khorana, 2019*

LMWH

Low GRADE	In adult ambulatory patients with malignancy initiating chemotherapy, thromboprophylaxis with LMWHs may result in a reduction in number of patients with a VTE, compared to placebo or standard of care. *Sources: Agnelli, 2009; Alexander, 2023; Altinbas, 2004; Kakkar, 2004; Macbeth, 2016; Perry, 2010 and Sideras, 2006*

Major bleeding

DOAC

Low GRADE	In adult ambulatory patients with malignancy initiating chemotherapy and an intermediate to high risk Khorana-score and no risk factors for bleeding, thromboprophylaxis with DOACs may result in little to no difference in number of patients with a major bleeding, compared to placebo. *Sources: Carrier, 2019 and Khorana, 2019*

LMWH

Very low GRADE	The evidence is very uncertain about the effect of thromboprophylaxis with LMWHs on the outcome major bleeding when compared with placebo or standard of care in adult ambulatory patients with malignancy initiating chemotherapy.

	Sources: Alexander, 2023; Agnelli, 2009; Kakkar, 2004; Macbeth, 2016; Perry, 2010 and Sideras, 2006

Clinically relevant non-major bleeding (CRNMB)

DOAC

Low GRADE	In adult ambulatory patients with malignancy initiating chemotherapy and an intermediate to high risk Khorana-score and no risk factors for bleeding, thromboprophylaxis with DOACs may result in little to no difference in number of patients with a CRNMB, compared to placebo. *Source: Carrier, 2019 and Khorana, 2019*

LMWH

Very low GRADE	The evidence is very uncertain about the effect of thromboprophylaxis with LMWHs on the outcome CRNMB when compared with standard of care in adult ambulatory patients with malignancy initiating chemotherapy and a high risk on thrombosis. *Source: Alexander, 2023*

Arterial thromboembolism

DOAC

Very low GRADE	The evidence is very uncertain about the effect of thromboprophylaxis with DOACs on the outcome ATE when compared with placebo in adult ambulatory patients with malignancy initiating chemotherapy and an intermediate to high risk Khorana-score and no risk factors for bleeding. *Source: Carrier, 2019 and Khorana, 2019*

LMWH

Very low GRADE	The evidence is very uncertain about the effect of thromboprophylaxis with LMWHs on the outcome ATE when compared with standard of care in adult ambulatory patients with malignancy initiating chemotherapy. *Source: Agnelli, 2009; Alexander, 2023 and Macbeth, 2016*

Quality of life

DOAC

No GRADE	None of the included studies on the effect of thromboprophylaxis with DOACs in patients with malignancy initiating chemotherapy reported on the outcome measure quality of life. Therefore, no conclusion can be drawn on the effect of thromboprophylaxis with DOACs on the outcome measure quality of life in adult ambulatory patients with malignancy initiating chemotherapy. *Sources: none*

LMWH

Very low GRADE	The evidence is very uncertain about the effect of thromboprophylaxis with LMWHs on the outcome measure quality of life when compared with placebo

	or standard of care in adult ambulatory patients with malignancy initiating chemotherapy. *Sources: Macbeth, 2016 and Sideras, 2006*

Discontinuation of oncological treatment/complementary treatments and quality of dying and death

No GRADE	None of the included studies reported on the outcome measures discontinuation of oncological treatment/complementary treatments and quality of dying and death. Therefore, no conclusion can be drawn on the effect of thromboprophylaxis with DOAC or LMWH on the outcome measures discontinuation of oncological treatment/complementary treatments and quality of dying and death in adult ambulatory patients with malignancy initiating chemotherapy. *Sources: none*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

DOACs

Ten opzichte van placebo zou tromboseprofylaxe met directe orale anticoagulantia (DOACs) kunnen leiden tot een *net clinical benefit* die klinisch relevant is bij volwassen patiënten met een maligniteit die starten met chemotherapie en die een gemiddeld tot hoog risico op een VTE hebben en geen risicofactoren voor een bloeding. De bewijskracht voor deze cruciale uitkomst is laag. Verder zijn we onzeker over het effect van tromboseprofylaxe met DOACs op de andere cruciale uitkomst mortaliteit (zeer laag GRADE). Voor beide uitkomsten wordt de bewijskrachtbeperkt vanwege het risico op bias en imprecisie.

Ook zijn we onzeker over de effecten van tromboseprofylaxe met DOACs op de belangrijke uitkomst arteriële trombo-embolie (ATE, zeer laag GRADE). De bewijskracht voor de belangrijke uitkomstmaten VTE, majeure bloeding en klinische niet relevante majeure bloeding is laag. Ten opzichte van placebo leidt tromboseprofylaxe mogelijk tot minder veneuze trombo-embolieën (VTE). Voor de uitkomstmaten majeure bloedingen en klinisch relevante niet majeure bloedingen is er mogelijk geen verschil tussen patiënten die tromboseprofylaxe met DOAC ontvingen, vergeleken met patiënten die een placebo kregen. Daarbij moet worden opgemerkt dat patiënten met risicofactoren op een bloeding of een eerdere bloeding werden uitgesloten. Geen van de studies rapporteerde over de uitkomstmaten kwaliteit van leven, aanvulling of stoppen van oncologische behandeling en kwaliteit van sterven en dood. Er kan derhalve geen conclusie worden getrokken over de effecten van tromboseprofylaxe met DOACs op de genoemde uitkomstmaten.

LMWH

Op basis van de geïncludeerde studies zijn we onzeker over het effect van tromboseprofylaxe met laagmoleculairgewicht heparine (LMWH) op de cruciale uitkomstmaten net clinical benefit en mortaliteit, vergeleken met placebo of geen tromboseprofylaxe bij volwassen patiënten met een maligniteit die starten met chemotherapie (zeer laag GRADE). De bewijskracht van de gevonden resultaten is erg beperkt vanwege het risico op bias, inconsistentie en imprecisie. De gegevens met betrekking tot de uitkomstmaat net clinical benefit waren beperkt; er waren slechts twee studies die voldoende gegevens rapporteerden om de net clinical benefit te kunnen berekenen. Dit bemoeilijkt de interpretatie van deze gegevens.

De bewijskracht voor de belangrijke uitkomstmaat VTE is laag. Ten opzichte van placebo of standaardzorg leidt tromboseprofylaxe met LMWH mogelijk tot minder VTE. Verder zijn we onzeker over het effect van tromboseprofylaxe met LMWH op de belangrijke uitkomstmaten ATE, majeure bloeding, klinische relevante niet majeure bloeding en kwaliteit van leven. Ook hiervoor geldt dat de bewijskracht beperkt werd door het risico op bias, inconsistentie en imprecisie.
Geen van de studies rapporteerde over de uitkomstmaten aanvulling of stoppen van oncologische behandeling en kwaliteit van sterven en dood. Er kan derhalve geen conclusie worden getrokken over de effecten van tromboseprofylaxe met LMWH op de genoemde uitkomstmaten.

Fondaparinux
Er zijn geen studies gevonden die de effectiviteit van tromboseprofylaxe met fondaparinux onderzochten bij patiënten met een maligniteit die startten met systeemtherapie.

Selectie van patiënten en generaliseerbaarheid
Het risico op VTE verschilt zeer sterk tussen patiëntengroepen. Het nut (meestal uitgedrukt als Number Needed tot Treat (NNT)) van tromboseprofylaxe hangt in belangrijke mate af van dit uitgangsrisico op VTE. Het risico is met name hoger bij patiënten met lokaal gevorderde of gemetastaseerde maligniteit en bij patiënten met een hoog-risico tumor, zoals een maag- of pancreascarcinoom. De meest gebruikte risicoscore om hoog-risico patiënten te identificeren is de Khorana score. Het voordeel van de Khorana score is dat deze goed gevalideerd is en makkelijk te berekenen is o.b.v. tumortype, bloedbeeld en BMI. Het nadeel is dat de discriminerende waarde beperkt is en dat de sensitiviteit en specificiteit variëren tussen tumortypen. In het onderzoek van Alexander (2023, TARGET-TP) werden hoog-risico patiënten geïdentificeerd op basis van D-dimeer en fibrinogeenconcentraties, maar deze manier van risicostratificatie is niet gevalideerd.

In de twee DOAC-trials werden enkel patiënten geïncludeerd met een Khorana score van twee of hoger (Carrier, 2019 en Khorana, 2019). Als deze trials als uitgangspunt worden genomen, dan heeft iedere aanbeveling over DOACs dus automatisch ook betrekking op het gebruik van de Khorana score om hoog-risico patiënten te identificeren. Door gebruik van de Khorana score werd een groep patiënten geselecteerd met een uitgangsrisico van 9.3% in zes maanden (cumulatieve incidentie VTE in placebogroepen: 65/696 = 9.3%). Dit komt goed overeen met de zes-maanden incidentie van 8.9% die werd geschat in een meta-analyse (Mulder, 2019). Bij gebruik van een afkapwaarde van drie punten stijgt de zes-maanden incidentie naar 11%. In deze groep is het nut van tromboseprofylaxe groter (Bosch, 2020).

In één van de DOAC trials (Khorana, 2019) werden patiënten geëxcludeerd bij wie een DVT van het been werd geconstateerd bij een screeningsecho vóór randomisatie; dit betrof 4.5% van de patiënten. Ook werd een screenende echo verricht na acht, 16 en 26 weken. Een asymptomatisch proximale DVT werd hierbij geconstateerd bij 4.3% in de placebogroep en 2.1% in de rivaroxaban groep. Dit beperkt de generaliseerbaarheid van de uitkomsten van deze studie, aangezien in de Nederlandse praktijk geen screenende echografie wordt toegepast. Het is onbekend of het effect van rivaroxaban groter of kleiner was geweest als screening voorafgaand aan randomisatie en tijdens het onderzoek níet was toegepast.

In de DOAC-trials werden patiënten geïncludeerd met een solide maligniteit of maligne lymfoom die gingen starten met nieuwe chemotherapie of andere systemische kankertherapie (behoudens hormoontherapie als monotherapie). Het is niet gerapporteerd welk deel van de patiënten neoadjuvante, adjuvante of palliatieve behandeling kregen.

Hoewel het overgrote deel van de patiënten behandeld werd met chemotherapie, is de werkgroep van mening dat de resultaten ook toepasbaar zijn op patiënten die andere vormen van systemische kankerbehandeling krijgen, zoals immuuntherapie of tyrosine kinase remmers, aangezien deze behandelingen geassocieerd zijn met een gelijk dan wel hoger tromboserisico. Aangezien er niet tot nauwelijks patiënten met acute leukemie of multipel myeloom werden geïncludeerd, kunnen de resultaten niet naar deze groepen vertaald worden. Overigens krijgen patiënten met multipel myeloom meestal reeds tromboseprofylaxe aangeboden op basis van patiënt- en behandeling specifieke criteria conform hematologische richtlijnen.

Patiënten met een verhoogd risico op bloedingen werden uitgesloten van deelname. Er zijn geen gevalideerde scores beschikbaar die specifiek bij patiënten met kanker het bloedingsrisico schatten. Bepaalde patiëntgroepen dienen doorgaans geen tromboseprofylaxe te krijgen vanwege het verhoogde risico op bloedingen of andere contra-indicaties (zie Tabel 3, welke grotendeels gebaseerd is op de exclusiecriteria van de trials die tromboseprofylaxe hebben onderzocht in patiënten met kanker i.c.m. internationale richtlijnen (Lyman, 2021)). Er dient opgemerkt te worden dat het baseline risico op bloedingen (met name gastrointestinale bloedingen) waarschijnlijk het hoogst is bij patiënten met een tumor van de slokdarm of maag in situ. Deze patiënten werden niet uitgesloten van de trials die tromboseprofylaxe onderzochten. Derhalve is de werkgroep van mening dat deze groep patiënten ook in aanmerking dient te komen voor tromboseprofylaxe. Een subgroepanalyse van de CASSINI-trial toonde dat ernstige bloedingen optraden bij 4 van 88 patiënten met een maagcarcinoom of gastro-oesofageaal carcinoom in de rivaroxaban groep (4.6%; waarvan 3 gastro-intestinale bloedingen) vergeleken met 1 van 85 patiënten in de placebogroep (1.2%) (HR 3.77; 95% BI 0.42-33.73; Mones, 2021). In de AVERT-trial ontwikkelde geen van de patiënten met een tumor van de bovenste tractus digestivus (n=44) of colorectaal carcinoom (n=11) een ernstige bloeding (Ladha, 2021).

Tabel 3: Overzicht risicofactoren voor bloedingen en contra-indicaties voor het starten van tromboseprofylaxe bij patiënten met een maligniteit die starten met systemische therapie.

Verhoogd bloedingsrisico
Bekende bloedingsziekte
Leverdysfunctie met coagulopathie (bv. verlengde PT en/of aPTT)
(Verwachte) trombopenie <50 x 10^9/L
eGFR <30 mL/min/1.73 m^2
Geplande stamceltransplantatie
Dubbele trombocytenaggregatieremming
Chronisch gebruik NSAID
Zeer laag lichaamsgewicht (<40 kg)
Gelijktijdig gebruik van sterke remmers van CYP3A4 of P-glycoproteine≠
Absolute contra-indicatie voor gebruik directe orale anticoagulantia
Zwangerschap
Borstvoeding
Relatieve contra-indicatie
Levensverwachting <6 maanden

*** Hiervoor kan gebruikt gemaakt worden van de tabellen uit de EHRA-Practical Guide to NOAC use in AF uit 2021 (Steffel, 2021). ≠ Bijvoorbeeld ketoconazol, itraconazol, voriconazol, posaconazol of HIV-proteaseremmers**

De meeste onderzoeken naar tromboseprofylaxe hadden een follow-up duur van zes maanden. De meeste VTE ontstaan in de eerste drie maanden na het starten van de kankerbehandeling. Het is derhalve onduidelijk of de voordelen van tromboseprofylaxe ook na zes maanden blijven bestaan. De werkgroep is echter van mening dat systemische kankerbehandeling een persisterende risicofactor is voor VTE, en dat tromboseprofylaxe dan ook gecontinueerd dient te worden tijdens de gehele behandeling, ook als deze langer dan zes maanden duurt, om het risico op een VTE na staken van tromboseprofylaxe te verlagen. De werkgroep is van mening dat bij patiënten bij wie de terminale palliatieve fase aanbreekt tromboseprofylaxe ook gestaakt dient te worden omdat het risico op bloedingen in deze fase groter lijkt dan het risico op trombose.

Net clinical benefit

Er is in deze module gekozen voor *net clinical benefit* als één van de cruciale uitkomstmaten. Hierdoor wordt naast een eventuele reductie in VTE ook de belangrijkste bijwerking van tromboseprofylaxe (majeure bloeding) meegewogen. Daarnaast kan tromboseprofylaxe in theorie een direct effect hebben op mortaliteit door het voorkómen van een fatale longembolie of het induceren van een fatale bloeding, en een indirect effect door het voorkómen van gevolgen van een VTE (bv. gecompliceerde ziekenhuisopname of bloeding door therapeutische antistolling). Daarbij moet aangetekend worden dat er geen bewijs is dat tromboseprofylaxe tot significante verbetering van overleving leidt (Schünemann, 2020). De beperking van de *net clinical benefit* is dat VTE en majeure bloeding binnen deze uitkomst een gelijke waarde hebben, terwijl dit voor de patiënt of arts niet zo hoeft te zijn. Daarnaast zijn andere relevante uitkomstmaten die beïnvloed kunnen worden door tromboseprofylaxe, zoals klinisch relevante niet-majeure bloedingen en ATE, geen onderdeel van de gebruikte definitie van *net clinical benefit*. Ook kan niet voor alle onderzoeken een net clinical benefit berekend worden doordat fatale bloedingen en VTE niet apart gerapporteerd worden, waardoor een risico staat op dubbele telling met mortaliteit.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>

Er is weinig onderzoek gedaan naar de waarden en voorkeuren van patiënten met betrekking tot tromboseprofylaxe. De uitkomst van de kankerbehandeling (bijvoorbeeld progressievrije overleving en mortaliteit) en kwaliteit van leven zijn voor de meeste patiënten met kanker doorgaans het belangrijkst. Aangezien VTE kan interfereren met de kankerbehandeling (bv. door een ziekenhuisopname of uitgestelde ingreep) en kan leiden tot morbiditeit (bv. pijn of dyspneu) is de werkgroep van mening dat het relevant is om het risico op VTE te bespreken en counseling over tromboseprofylaxe aan te bieden. Recent internationaal onderzoek laat echter zien dat 62% van de patiënten met kanker geen informatie had gekregen over het verhoogde risico op VTE en dat 69% geen informatie over symptomen passend bij VTE had gekregen (Potere, 2022).

Besluitvorming over tromboseprofylaxe dient expliciet gedeeld te worden met de patiënt. Er dient aangemerkt te worden dat er geen bewijs is dat tromboseprofylaxe tot verbetering van overleving leidt. Bij de counseling dient besproken te worden: het effect van tromboseprofylaxe op net clinical benefit, VTE en (majeure) bloedingen. Daarnaast dient de toedieningsvorm besproken te worden. Tromboseprofylaxe kan aangeboden worden middels LMWH (dagelijkse subcutane injecties) of DOACs (tabletten rivaroxaban 10 mg eenmaal daags of apixaban 2,5 mg tweemaal daags). Hoewel weinig onderzoek is gedaan naar het effect van subcutane injecties vs orale medicatie op de kwaliteit van leven, neemt de werkgroep aan dat patiënten (bij gelijke effectiviteit en veiligheid) een voorkeur zullen hebben voor orale medicatie, mits orale medicatie mogelijk is.

Kosten (middelenbeslag)

Er is geen kosteneffectiviteitsanalyse gedaan naar tromboseprofylaxe voor poliklinische patiënten met kanker in de Nederlandse setting. In een onderzoek uit Spanje werd geschat dat tromboseprofylaxe met apixaban leidde tot een daling van de kosten met €64,- en een klinisch niet significante toename van 0.008 quality adjusted life years (QALY's) op de korte termijn (zes maanden, Muñoz, 2023). Tromboseprofylaxe middels rivaroxaban was geassocieerd met een stijging van de kosten met €121,- en een klinisch niet significante toename van 0.008 QALY's. Een Canadees onderzoek schatte dat tromboseprofylaxe middels apixaban geassocieerd is met een daling van de kosten met 257 CAD en een toename van 0.001 QALY's op de korte termijn (zes maanden) en een daling van 6.973 CAD en toename van 0.083 QALY's op de lange termijn (Kimpton, 2021). Tot slot toonde onderzoek uit de Verenigde Staten aan dat tromboseprofylaxe met rivaroxaban of apixaban leidde tot een toename in kosten van $1.445 en toename van 0.12 QALY's op de korte termijn (zes maanden) (Li, 2020)). Op basis van deze onderzoeken lijkt, voor de Nederlandse praktijk, tromboseprofylaxe middels apixaban en rivaroxaban niet tot onaanvaardbare zorgkosten te leiden, en waarschijnlijk een geringe toename in QALY's. Wat niet is meegewogen in de kosteneffectiviteitsanalyses, zijn de kosten die gepaard gaan met counseling van hoog-risico patiënten m.b.t. tromboseprofylaxe. De kosten van LMWH en DOACs in profylactische dosering zijn ten tijde van het opstellen van de richtlijn ongeveer gelijk, afhankelijk van het gekozen preparaat, waardoor er vanuit kostenperspectief geen duidelijke voorkeur is.

Aanvaardbaarheid, haalbaarheid en implementatie

Het bespreken van het risico op VTE en klachten passend bij VTE zou bij voorkeur onderdeel van het informatiegesprek met patiënten die starten met systemische kankerbehandeling moeten zijn. De praktijk leert echter dat het merendeel van de Nederlandse kankerbehandelaren het risico op VTE nooit of soms bespreken, en dat slechts een klein aantal de Khorana score kent en ook daadwerkelijk gebruikt (Kapteijn, 2022). Hieruit kan afgeleid worden dat counseling over tromboseprofylaxe momenteel zelden wordt aangeboden aan patiënten met kanker in Nederland. Mogelijke verklaringen hiervoor zijn dat (i) patiënten al veel informatie krijgen over de prognose, behandeling en andere complicaties, (ii) er niet voldoende tijd is voor het bespreken van het risico op VTE en counseling over tromboseprofylaxe, (iii) VTE niet beschouwd wordt als een relevante complicatie of (iv) dat kankerbehandelaren niet op de hoogte zijn van de literatuur over tromboseprofylaxe.

De resultaten uit de beschikbare gerandomiseerde onderzoeken suggereren dat er een mogelijk voordeel is van tromboseprofylaxe met beperkte belasting voor de patiënt (orale behandeling), is de werkgroep van mening dat counseling hierover routinematig aangeboden dient te worden aan hoog-VTE-risico patiënten zonder risicofactoren voor bloedingen die starten met systemische behandeling, bijvoorbeeld patiënten met een hoog-risico tumor, zoals maag- of pancreascarcinoom, of patiënten met een Khorana score van twee punten of hoger. Daarnaast dienen patiënten geïnformeerd te worden over de klachten en symptomen die kunnen duiden op een DVT of longembolie en, indien gekozen wordt voor tromboseprofylaxe, de klachten en symptomen die kunnen duiden op een bloeding. Deze informatievoorziening kan onderdeel zijn van het algemene informatiegesprek dat reeds voorafgaand aan het starten van een nieuwe behandeling wordt gevoerd. Tromboseprofylaxe dient doorgaans gestaakt te worden bij het optreden van ernstige bloedingen en bij het staken van de kankerbehandeling. Ook in andere situaties kan besloten worden dat het voordeel van tromboseprofylaxe niet meer opweegt tegen het risico op bloedingen, bijvoorbeeld bij het ontstaan van ernstige nierinsufficiëntie of trombopenie.

Aanbeveling

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

De werkgroep is van mening dat er op basis van lage bewijskracht een voordeel zou kunnen zijn van tromboseprofylaxe met een DOAC bij poliklinische patiënten met een solide maligniteit of maligne lymfoom die starten met systemische behandeling (o.a. chemotherapie, immuuntherapie of orale kankerbehandeling zoals tyrosine kinase remmers) en een hoog risico hebben op VTE en geen risicofactoren voor een bloeding. Dit voordeel bestaat uit een klinisch relevant lager risico op het gecombineerd eindpunt van VTE, ernstige bloedingen en mortaliteit. Dit eindpunt wordt gedreven door een klinisch relevant lager risico op VTE ten koste van een gering verhoogd risico op ernstige bloedingen, zonder een effect op mortaliteit. Het risico op VTE kan ingeschat worden met de Khorana score, waarbij patiënten met twee of meer punten geclassificeerd worden als 'hoog risico'. Patiënten met een verhoogd risico op bloedingen dienen geen tromboseprofylaxe te krijgen, zoals patiënten met (verwachte) diepe trombopenie, een eerdere klinisch relevante bloeding, moeilijk te behandelen ernstige hypertensie, hersenmetastasen of primaire hersentumor of een eGFR <30 mL/min/1.73 m^2. De werkgroep geeft de voorkeur aan een DOAC (tabletten rivaroxaban 10 mg eenmaal daags of apixaban 2,5 mg tweemaal daags) boven LMWH op basis van de aanvaardbaarheid voor patiënten (orale vs. subcutane toediening) bij gelijke kosten. Indien orale toediening niet mogelijk is of er contra-indicaties zijn voor een DOAC of belangrijke interacties met andere medicatie, kan LMWH als alternatief gegeven worden, hoewel het effect van LMWH op het net clinical benefit zeer onzeker is. De werkgroep schat in dat de kosteneffectiviteit van tromboseprofylaxe met een DOAC voor de Nederlandse maatschappij acceptabel is o.b.v. extrapolatie van buitenlandse kosteneffectiviteitsanalyses. Ondanks dat de onderzoeken een follow-up duur hadden van maximaal zes maanden, is de werkgroep van mening dat overwogen moet worden de tromboseprofylaxe te continueren gedurende de duur van de systemische kankerbehandeling, aangezien het risico op VTE verhoogd blijft is en blijft tijdens kankerbehandeling. Daarnaast is de werkgroep van mening dat tromboseprofylaxe gestaakt dient te worden als er contra-indicaties optreden (bijvoorbeeld ernstige trombopenie, ernstige nierinsufficiëntie, ernstige hypertensie of ernstige bloedingen). Het besluit omtrent tromboseprofylaxe (zowel start als stop) dient zeer nadrukkelijk genomen te worden samen met de patiënt ('gedeelde besluitvorming'). Daarnaast dienen patiënten voorlichting te krijgen over het verhoogde risico op VTE en klachten passend bij een DVT of longembolie, zodat adequate diagnostiek tijdig ingezet kan worden, en over het risico op bloedingen als gekozen wordt voor tromboseprofylaxe.

Licht patiënten die starten met systemische kankerbehandeling voor over het verhoogde risico op veneuze trombo-embolie en klachten passend bij een DVT of longembolie.

Overweeg counseling aan te bieden over tromboseprofylaxe in de vorm van een DOAC (apixaban 2,5 mg 2dd of rivaroxaban 10 mg 1dd) aan poliklinische patiënten met een solide maligniteit of maligne lymfoom en een hoog risico op veneuze trombo-embolie (Khorana score ≥2 punten) die starten met systemische kankerbehandeling (exclusief monotherapie met hormonale therapie) en geen risicofactoren hebben voor een bloeding (zie Tabel 3).

Overweeg tromboseprofylaxe te continueren na de eerste 6 maanden, en pas te stoppen bij het beëindigen van de systemische kankerbehandeling.

Stop tromboseprofylaxe bij het optreden van klinisch relevante bloedingen, als er een hoog risico op bloedingen ontstaat of als de terminale fase aanbreekt.

Kennisvragen

De aanbeveling is grotendeels gebaseerd op twee RCTs die apixaban en rivaroxaban onderzochten. Belangrijke kennislacunes zijn de net clinical benefit van de interventie in verschillende groepen (bv. gestratificeerd naar tumortype en Khorana score 2 vs >=3). Daarnaast is onduidelijk wat het effect van rivaroxaban is in de Nederlandse populatie aangezien er in de RCTs gebruik werd gemaakt van echografische screening naar asymptomatische DVT voorafgaand aan randomisatie en tijdens follow-up. Er is geen gedegen onderzoek gedaan naar het effect van tromboseprofylaxe op de kwaliteit van leven en naar de voorkeuren. Voorts is geen kosteneffectiviteitsanalyse in Nederland uitgevoerd en is in de internationale kosteneffectiviteitsanalyses geen rekening gehouden met de kosten van counseling.

Dit levert de volgende onderzoeksvragen op:

- Wat is de net clinical benefit van tromboseprofylaxe met DOACs (apixaban en rivaroxaban) bij patiënten met een maligniteit die starten met systemische behandeling, gestratificeerd naar bijv. tumortype, Khorana score 2 vs >=3?
- Wat is het effect van tromboseprofylaxe met rivaroxaban bij volwassenen met een maligniteit die starten met een systemische behandeling, in de Nederlandse setting, aangezien screening naar DVT voorafgaand aan kankerbehandeling en tijdens de behandeling hier niet verricht wordt?
- Wat geven patiënten aan als voorkeur t.a.v een profylactische behandeling ter voorkoming van VTE in deze setting en wat is het effect op de kwaliteit van leven?
- Wat is de kosteneffectiviteit in Nederland en wat zijn de kosten gerelateerd aan voorlichting in deze setting?

Literatuur

Agnelli G, Gussoni G, Bianchini C, Verso M, Mandalà M, Cavanna L, Barni S, Labianca R, Buzzi F, Scambia G, Passalacqua R, Ricci S, Gasparini G, Lorusso V, Bonizzoni E, Tonato M; PROTECHT Investigators. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. Lancet Oncol. 2009 Oct;10(10):943-9. doi: 10.1016/S1470-2045(09)70232-3. Epub 2009 Aug 31. PMID: 19726226.

Altinbas M, Coskun HS, Er O, Ozkan M, Eser B, Unal A, Cetin M, Soyuer S. A randomized clinical trial of combination chemotherapy with and without low-molecular-weight heparin in small cell lung cancer. J Thromb Haemost. 2004 Aug;2(8):1266-71. doi: 10.1111/j.1538-7836.2004.00871.x. PMID: 15304029.

Bosch FTM, Mulder FI, Kamphuisen PW, Middeldorp S, Bossuyt PM, Büller HR, van Es N. Primary thromboprophylaxis in ambulatory cancer patients with a high Khorana score: a systematic review and meta-analysis. Blood Adv. 2020 Oct 27;4(20):5215-5225. Doi: 10.1182/bloodadvances.2020003115. PMID: 33104795; PMCID: PMC7594395.

Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, Kuruvilla P, Hill D, Spadafora S, Marquis K, Trinkaus M, Tomiak A, Lee AYY, Gross PL, Lazo-Langner A, El-Maraghi R, Goss G, Le Gal G, Stewart D, Ramsay T, Rodger M, Witham D, Wells PS; AVERT Investigators. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. N Engl J Med. 2019 Feb 21;380(8):711-719. doi: 10.1056/NEJMoa1814468. Epub 2018 Dec 4. PMID: 30511879.

Kakkar AK, Levine MN, Kadziola Z, Lemoine NR, Low V, Patel HK, Rustin G, Thomas M, Quigley M, Williamson RC. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). J Clin Oncol. 2004 May 15;22(10):1944-8. doi: 10.1200/JCO.2004.10.002. PMID: 15143088.

Kaptein FHJ, Guman NAM, van Es N, Kamphuisen PW, Klok FA, Mairuhu ATA, Huisman MV. Treatment and prevention of cancer-associated thrombosis in the Netherlands: A national survey. Res Pract Thromb Haemost. 2023 Jan 24;7(1):100057. Doi: 10.1016/j.rpth.2023.100057. PMID: 36846646; PMCID: PMC9943872.

Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, Streiff MB, Garcia DA, Liebman HA, Belani CP, O'Reilly EM, Patel JN, Yimer HA, Wildgoose P, Burton P, Vijapurkar U, Kaul S, Eikelboom J, McBane R, Bauer KA, Kuderer NM, Lyman GH; CASSINI Investigators. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. N Engl J Med. 2019 Feb 21;380(8):720-728. doi: 10.1056/NEJMoa1814630. PMID: 30786186.

Kimpton M, Kumar S, Wells PS, Coyle D, Carrier M, Thavorn K. Cost-utility analysis of apixaban compared with usual care for primary thromboprophylaxis in ambulatory patients with cancer. CMAJ. 2021 Oct 12;193(40):E1551-E1560. Doi: 10.1503/cmaj.210523. PMID: 35040802; PMCID: PMC8568073.

Ladha D, Mallick R, Wang TF, Caiano L, Wells PS, Carrier M. Efficacy and safety of apixaban for primary prevention in gastrointestinal cancers: A post-hoc analysis of the AVERT trial. Thromb Res. 2021 Jun;202:151-154. doi: 10.1016/j.thromres.2021.03.013. Epub 2021 Mar 21. PMID: 33857789.

Li A, Carlson JJ, Kuderer NM, Schaefer JK, Li S, Garcia DA, Khorana AA, Carrier M, Lyman GH. Cost-effectiveness analysis of low-dose direct oral anticoagulant (DOAC) for the prevention of cancer-associated thrombosis in the United States. Cancer. 2020 Apr 15;126(8):1736-1748. Doi: 10.1002/cncr.32724. Epub 2020 Jan 30. PMID: 31999844.

Lyman GH, Carrier M, Ay C, Di Nisio M, Hicks LK, Khorana AA, Leavitt AD, Lee AYY, Macbeth F, Morgan RL, Noble S, Sexton EA, Stenehjem D, Wiercioch W, Kahale LA, Alonso-Coello P. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv. 2021 Feb 23;5(4):927-974. Doi: 10.1182/bloodadvances.2020003442. Erratum in: Blood Adv. 2021 Apr 13;5(7):1953. PMID: 33570602; PMCID: PMC7903232.

Macbeth F, Noble S, Evans J, Ahmed S, Cohen D, Hood K, Knoyle D, Linnane S, Longo M, Moore B, Woll PJ, Appel W, Dickson J, Ferry D, Brammer C, Griffiths G. Randomized Phase III Trial of Standard Therapy Plus Low Molecular Weight Heparin in Patients With Lung Cancer: FRAGMATIC Trial. J Clin Oncol. 2016 Feb 10;34(5):488-94. doi: 10.1200/JCO.2015.64.0268. Epub 2015 Dec 23. PMID: 26700124.

Mones JV, Streiff MB, Khorana AA, Bendheim GA, Damaraju CV, Wildgoose P, Burton P, Riess H, Soff GA. Rivaroxaban thromboprophylaxis for gastric/gastroesophageal junction tumors versus other tumors: A post hoc analysis of the randomized CASSINI trial. Res Pract Thromb Haemost. 2021 Jul 20;5(5):e12549. doi: 10.1002/rth2.12549. PMID: 34308096; PMCID: PMC8292144.

Mulder FI, Horváth-Puhó E, van Es N, van Laarhoven HWM, Pedersen L, Moik F, Ay C, Büller HR, Sørensen HT. Venous thromboembolism in cancer patients: a population-based cohort study. Blood. 2021 Apr 8;137(14):1959-1969. doi: 10.1182/blood.2020007338. PMID: 33171494.

Mulder FI, Candeloro M, Kamphuisen PW, Di Nisio M, Bossuyt PM, Guman N, Smit K, Büller HR, van Es N; CAT-prediction collaborators. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. Haematologica. 2019 Jun;104(6):1277-1287. doi: 10.3324/haematol.2018.209114. Epub 2019 Jan 3. PMID: 30606788; PMCID: PMC6545838.

Muñoz AJ, Ortega L, Gutiérrez A, Gallardo E, Rubio-Rodríguez D, Rubio-Terrés C, Morón B, García-Alfonso P, Soria JM. Cost-effectiveness of apixaban and rivaroxaban in thromboprophylaxis of cancer patients treated with chemotherapy in Spain. J Med Econ. 2023 Jan-Dec;26(1):1145-1154. doi: 10.1080/13696998.2023.2248839. Epub 2023 Aug 21. PMID: 37602646.

Perry JR, Julian JA, Laperriere NJ, Geerts W, Agnelli G, Rogers LR, Malkin MG, Sawaya R, Baker R, Falanga A, Parpia S, Finch T, Levine MN. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. J Thromb Haemost. 2010 Sep;8(9):1959-65. doi: 10.1111/j.1538-7836.2010.03973.x. PMID: 20598077.

Potere N, Barco S, Mahé I, Cesarman-Maus G, Angchaisuksiri P, Leader A, Okoye HC, Olayemi E, Ay C, Carrier M, Connors JM, Farmakis IT, Fumagalli RM, Jing ZC, Lee LH, McLintock C, Ní Ainle F, Giannakoulas G, Goto S, Guillermo Esposito MC, Jara-Palomares L, Szlaszynska M, Tan CW, Van Es N, Wang TF, Hunt BJ, Di Nisio M. Awareness of venous thromboembolism among patients with cancer: Preliminary findings from a global initiative for World Thrombosis Day. J Thromb Haemost. 2022 Dec;20(12):2964-2971. doi: 10.1111/jth.15902. Epub 2022 Oct 21. PMID: 36201366; PMCID: PMC9828201.

Rutjes AW, Porreca E, Candeloro M, Valeriani E, Di Nisio M. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database Syst Rev. 2020 Dec 18;12(12):CD008500. doi: 10.1002/14651858.CD008500.pub5. PMID: 33337539; PMCID: PMC8829903.

Schünemann HJ, Ventresca M, Crowther M, Briel M, Zhou Q, Noble S, Macbeth F, Griffiths G, Garcia D, Lyman GH, Di Nisio M, Iorio A, Mbuagbaw L, Neumann I, van Es N, Brouwers M, Guyatt G, Streiff MB, Marcucci M, Baldeh T, Florez ID, Alma OG, Solh Z, Bossuyt PM, Kahale LA, Ageno W, Bozas G, Büller HR, Lebeau B, Lecumberri R, Loprinzi C, McBane R, Sideras K, Maraveyas A, Pelzer U, Perry J, Klerk C, Agnelli G, Akl EA. Evaluating prophylactic heparin in ambulatory patients with solid tumours: a systematic review and individual participant data meta-analysis. Lancet Haematol. 2020 Oct;7(10):e746-e755. doi: 10.1016/S2352-3026(20)30293-3. PMID: 32976752.

Sideras K, Schaefer PL, Okuno SH, Sloan JA, Kutteh L, Fitch TR, Dakhil SR, Levitt R, Alberts SR, Morton RF, Rowland KM, Novotny PJ, Loprinzi CL. Low-molecular-weight heparin in patients with advanced cancer: a phase 3 clinical trial. Mayo Clin Proc. 2006 Jun;81(6):758-67. doi: 10.4065/81.6.758. PMID: 16770976.

Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Vanassche T, Potpara T, Camm AJ, Heidbüchel H; External reviewers. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021 Oct 9;23(10):1612-1676. doi: 10.1093/europace/euab065. Erratum in: Europace. 2021 Oct 9;23(10):1676. doi: 10.1093/europace/euab157. PMID: 33895845.

Bijlagen bij module tromboseprofylaxe bij volwassenen met een maligniteit

Implementatietabel

5 Verkeerslichtanalyse

15

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	**Sterkte van de aanbeveling**	**Bewijskracht per uitkomstmaat**	**Verkeerslicht per (sub)aanbeveling**
Licht patiënten die starten met systemische kankerbehandeling voor over het verhoogde risico op veneuze trombo-embolie en klachten passend bij een DVT of longembolie. Overweeg counseling aan te bieden over tromboseprofylaxe in de vorm van een DOAC (apixaban 2,5 mg 2dd of rivaroxaban 10 mg 1dd) aan poliklinische patiënten met een solide maligniteit of maligne lymfoom en een hoog risico op veneuze trombo-embolie (Khorana score ≥2 punten) die starten met systemische kankerbehandeling (exclusief monotherapie met hormonale therapie) en geen risicofactoren hebben voor een bloeding (zie Tabel 3). Overweeg tromboseprofylaxe te continueren na de eerste 6 maanden, en pas te stoppen bij het beëindigen van de systemische kankerbehandeling.	□ Sterk (doe/ gebruik) / **X** Zwak (overweeg)	**Overal bewijskracht** □ **H** □ **M** □ **L** **X VL** □ **NG** **Range bewijskracht van alle uitkomstmaten** □ **H** □ **M** **X L** **X VL** □ **NG** **OF** □ **voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in **X ORANJE:** gebruik tabel B □ **LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in

Stop tromboseprofylaxe bij het optreden van klinisch relevante bloedingen, als er een hoog risico op bloedingen ontstaat of als de terminale palliatieve fase aanbreekt.			

Implementatietabel

Op basis van de beschikbare evidentie en ervaring uit de praktijk kon er onvoldoende richting aan de besluitvorming worden gegeven. Om die reden is er geen beschrijving van belemmeringen en kansen voor implementatie van de aanbeveling toegevoegd. Disseminatie van de kennis in deze module verloopt via de standaard route. De module wordt gepubliceerd op de Richtlijnendatabase.

Evidence tables

Evidence table for systematic review of RCTs and observational studies (intervention studies)

Research question: What are the (un)desirable effects of thromboprophylaxis with Direct Oral Anticoagulants (DOAC), Low-Molecular-Weight Heparin (LMWH) or fondaparinux in adult ambulatory patients with malignancy in which systemic anticancer treatment was initiated, compared to placebo or standard of care?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Rutjes, 2020 Study characteristics and results are extracted from the SR, for details see study characteristics in Rutjes (2020).	SR and meta-analysis of RCTs *Literature search up to August 2020* **A**: Agnelli, 2009 **D:** Altinbas, 2004 **E**: Vadhan-Raj, 2013 **F**: Sideras, 2006 **G**: Kakkar, 2004 **H**: Perry, 2010 **I**: Macbeth, 2016 (TOPIC-2) **K:** Khorana 2019 **L:** Carrier, 2019 <u>Study design</u>: Parallel RCT's, all included studies **I:** superiority trial <u>Setting and Country</u>: **A**: multicenter, EU	Inclusion criteria SR: RCT's and quasi-RCT's on participants who were ambulatory patients receiving chemotherapy at the time of randomisation or study entry. Intervention: Any type of oral or parenteral coagulation. Exclusion criteria SR: Studies of participants receiving anticoagulation for a previous VTE or an indication other than VTE. Studies evaluating prophylaxis for catheter-related thrombosis. *Total of 32 studies included in qualitive analysis, 19 studies*	**A**: Nadroparin, 3800 IU SC, once daily for max. 120 days or for whole duration of chemotherapy **D**: Dalteparin, 5000 IU SC, once daily for whole duration of therapy (was stopped with disease progression or at end of 18wks chemo) **E**: Dalteparin, 5000 IU SC once daily for 16 weeks + standard care **F**: Dalteparin, 5000 IU SC for 18 weeks or until disease progression **G**: Dalteparin, 5000 IU SC, once daily for 1 year or until death **H**: Dalteparin, 5000 IU SC, once daily,	**A**: Placebo **D:** no dalteparin **E**: Standard care **F**: First part placebo, second part standard care alone **G**: Placebo **H**: Placebo, median duration 157 days **I**: Standard care **K:** Placebo **L:** Placebo	<u>End-point of follow-up (median)</u>: **A:** I 111 days, C: 113 days **D:** 10 (2-33) months **E**: NR **F**: NR, 18 months was planned **G**: I: 10 months, C: 9 months **H**: NR, 12 months was planned **I**: 23.1 (IQR 3.6-31.2) months **K:** NR **L:** 183 days <u>For how many participants were no complete outcome data available?</u> **A**: NR **D:** NR **E**: NR **F**: NR **G**: NR **H**: NR **I**: NR **K:** NR **L:** NR	*For all analyses: pooled effect is NA (since not all of the studies in Rutjes (2020) will be included in our analysis*. <u>Symptomatic VTE</u> Defined as objectively verified by means of Doppler (compression) ultrasonography or venography for DVT, and spiral computed tomography, ventilation/perfusion lung scan, or pulmonary angiography for PE. *DOAC (RR (95%CI))* **K:** 0.79 [0.41 , 1.54] **L:** 0.39 [0.18 , 0.83] *LMWH (RR (95%CI))* **F:** 0.41 [0.08 , 2.05] **G:** 2.91 [0.12 , 70.87] **H:** 4.39 [0.52 , 36.89]	<u>Author's conclusion</u> In ambulatory cancer patients, primary thromboprophylaxis with direct factor Xa inhibitors may reduce the incidence of symptomatic venous thromboembolism (VTE) (low-certainty evidence) and probably increases the risk major bleeding (moderate-certainty evidence) when compared with placebo. Low-molecular-weight heparin (LMWH) reduces symptomatic VTE with 37 participants requiring prophylaxis to prevent one event (high-certainty evidence). This benefit comes at the cost of a higher incidence of major bleeding, where for each 144 participants treated, one event is expected to occur when compared against

	D: NR **E**: NR, USA **F**: multicenter, USA **G**: multicenter, USA **H**: multicenter, western countries **I**: multicenter, UK **K:** multicenter, USA **L:** multicenter, Canada <u>Source of funding and conflicts of interest:</u> **A**: Commercial funding by pharmaceutical company, scientific director of pharmaceutical company was involved as author **D:** Funding source not reported, no disclosure of potential COI **E**: NR (commercial partner listed at clinicaltrials.gov) **F**: Non-commercial funding, COI NR **G**: Commercial funding by pharmaceutical company, several COI reported. **H**: Commercial funding by pharmaceutical	*included in meta-analysis. Since part of these studies did not fulfil our inclusion criteria, we described 12 studies in this evidence table.* <u>Important patient characteristics at baseline</u>: <u>N</u> **A**: I: 779, C: 387 **D:** 83 **E**: I: 38, C: 37 **F**: first part: n=52, second part: n=86 **G**: I: 196, C: 189 **H**: I: 98, C: 88 **I**: I: 102, C: 1101 **K:** I: 436, C: 421 **L:** I: 291, C: 283 <u>Age (mean years±SD)</u> **A**: I 62.1 (10.3) C: 63.7 (9.2) **D:** median 58 (IQR 34-75) **E**: I: 59 (range 36-75), C: 64 (38-77) **F**: First part: I: 64.5 (NR), C: 63.5 (NR) Second part: I: 68.5 (NR), C: 70.5 (NR) **G**: I: 62 (IQR 54-68), C: 60.9 (IQR 52-69)) **H**: I: 57 (range 30-81), C: 55 (range 26-77) **I**: median I: 65 (IQR 59-71), C: 64 (IQR 58-71)	median duration 183 days. **I**: Dalteparin, 5000 IU SC once daily for 24 weeks plus standard care **K:** Rivaroxaban,10 mg once daily up to 180 days, mean treatment period was 4.3 months **L:** Apixaban, 2.5 mg twice daily for 6 months			**I:** 1.50 [0.62 , 3.66] *Fondaparinux* NA <u>Any VTE</u> Defined as symptomatic and incidental VTE *DOAC (RR (95%CI))* **K:** 0.68 [0.42 , 1.10] **L:** 0.41 [0.21 , 0.79] *LMWH (RR (95%CI))* **A:** 0.56 [0.29 , 1.08] **E:** 0.22 [0.05 , 0.94] **I:** 0.57 [0.42 , 0.77] *Fondaparinux* NA <u>Major bleed</u> Defined as overt bleeding associated with a decrease in haemoglobin of 2 g/dL or more, or leading to a transfusion of two or more units of packed red blood cells or whole blood; bleeding that occurred at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular,intramuscular with compartment syndrome, retroperitoneal); or bleeding contributing to death. *DOAC (RR (95%CI))* **K:** 2.00 [0.61 , 6.57] **L:** 1.91 [0.66 , 5.52]	placebo or no thromboprophylaxis (moderate-certainty evidence). When deciding whether to use primary antithrombotic prophylaxis in ambulatory cancer patients receiving chemotherapy, clinicians need to determine the patient's baseline risk of VTE with the help of risk-stratification models and weigh the magnitude of benefit with antithrombotic prophylaxis, especially on major clinical endpoints, against the risk of major bleeding complications. Evidence for the use of thromboprophylaxis with anticoagulants other than direct factor Xa inhibitors and LMWH is limited. <u>Remarks on individual studies</u> **F**: After 52 accrued participants, the study was modified because of concerns that the low accrual rate was related to the requirements for placebo injections. The saline placebo injections were eliminated, then, unblinded LMWH was compared with standard clinical care. **I:** The trial did not reach its intended number of events for the primary analysis. Use

	companies, lead author reported COI **I**: Partial commercial funding by pharmaceutical company, some authors reported COI **K:** Partial commercial funding by pharmaceutical companies, all authors reported COI. **L:** Partial commercial funding by pharmaceutical companies, all authors reported COI	**K:** I: median 63(range 23-88), C: 62 (range 28-88) **L:** I: 61.2 (12.4), C: 61.7 (11.3) *Sex (% male):* **A**: 48 **D:** 82 **E**: I: 52.6, C: 56.8 **F**: First part: I: 50, C: 42 Second part: I: 64, C: 70 **G**: I: 40.5, C: 45.7 **H**: I: 62, C: 57 **I**: I: 60, C: 59.6 **K:** I: 52.9, C: 48.9 **L:** I: 41.6, C: 42 *Metastatic disease (%):* **A**: NR **D:** I: n=19, C: n=17 **E**: NR **F**: NR (all incurable cancer) **G**: I: 85, C: 87.5 **H**: NR **I**: I: 60.9, C: 60.5 **K:** NR (54.5) in those with solid tumour **L:** I: 73 (25.1), C: 67 (23.7) *Previous VTE (n (%)):* **A**: I: 12 (1.6), C: 6 (1.6) **D:** 0 (NA) **E**: NR **F**: First part: I: 4, C: 4 Second part: I: 5, C: 0 **G**: 0 (NA) **H**: NR **I**: NR **K:** I: 13 (3.1), C: 2 (0.5)				*LMWH (RR (95%CI))* **F:** 0.41 [0.08 , 2.05] **G:** 2.91 [0.12 , 70.87] **H:** 4.39 [0.52 , 36.89] **I:** 1.50 [0.62 , 3.66] *Fondaparinux* NA Clinically relevant bleeding Defined as major and clinically relevant nonmajor bleeding); typically defined as overt bleeding that does not meet the criteria for major bleeding, but is associated with the need for medical intervention, contact with a physician, or interruption of the study drug or with discomfort or impairment of activities of daily life *DOAC (RR (95%CI))* **K:** 1.58 [0.78 , 3.21] *LMWH (RR (95%CI))* **I:** 4.43 [2.49 , 7.86] *Fondaparinux* NA Mortality Defined as 1 year overall mortality *DOAC (RR (95%CI))* **NA** *LMWH (RR (95%CI))* **D:** 0.64 [0.43 , 0.97]	of prophylactic anticoagulant outside of trial (short-term use, e.g. inpatient thromboprophylaxis, and therapeutic anticoagulation were allowed if clinically indicated according to local guidelines), n (%): 106 (9.7%) in LMWH group; 88 (8.0%) in control group.

		L: 9 (3.1), 8 (2.8) <u>*Disease characteristics*</u> **A:** Ambulatory patients receiving chemotherapy for metastatic or locally advanced lung, gastrointestinal, pancreatic, breast, ovarian, or head and neck cancer **D:** small-cell lung carcinoma patients with ECOG performance status of <3 and normal haematological, renal, and hepatic function tests **E**: Patients with advanced stage adenocarcinoma of the pancreas planning to initiate systemic chemotherapy within 2 weeks, ECOG performance status 0–2, adequate renal function. **F**: Patients with advanced breast cancer who had failed first-line chemotherapy; advanced prostate cancer who had failed primary hormonal therapy; advanced lung cancer; or advanced colorectal cancer.				**F:** 1.13 [0.87 , 1.47] **G:** 0.91 [0.76 , 1.08] **H:** 1.24 [0.87 , 1.75] *Fondaparinux* NA <u>Quality of life</u> Defined as *DOAC (RR (95%CI))* **NA** *LMWH (RR (95%CI))* **F:** 1.06 [0.77 to 1.45] *LMWH (MD (95%CI))* **I** (6 months): 0.11 (-3.18 to 3.40) **I** (12 months): –0.34 (–5.25 to 4.57) *Fondaparinux* NA <u>Arterial thromboembolic events.</u> Defined as *DOAC (RR (95%CI))* **K:** 0.57 [0.17 , 1.94] *LMWH (RR (95%CI))* **A:** 0.50 [0.10 , 2.44] **I:** 0.92 [0.53 , 1.60] *Fondaparinux* NA	

		G: patients with advanced stage III or IV malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary, or uterus. **H**: Patients with grade 3 or grade 4 Glioma **I**: Patients with primary bronchial carcinoma of any stage and histology **K:** High-risk ambulatory patients with solid cancer or lymphoma who had a Khorana score of ≥ 2, had a plan to start a new systemic regimen within 1 week before or after initiating the trial regimen and had no DVT on screening ultrasonography. **L:** Patients with a newly diagnosed cancer site or progression of the malignant disease after complete or partial remission who were initiating a new course of chemotherapy with a minimum intent of 3 months' therapy and who had a Khorana score of ≥ 2. Groups comparable at baseline? Yes					

Evidence table for systematic review of RCTs and observational studies (intervention studies)

Research question: What are the (un)desirable effects of thromboprophylaxis with Direct Oral Anticoagulants (DOAC), Low-Molecular-Weight Heparin (LMWH) or fondaparinux in adult ambulatory patients with malignancy in which systemic anticancer treatment was initiated, compared to placebo or standard of care?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size [4]	Comments
Alexander, 2023	Type of study: Open-label RCT Setting and country: Metropolitan (N=1) and regional (N=4) hospitals, Australia Funding and conflicts of interest: Several authors reported COI.	Inclusion criteria: Adults with clinician-estimated life expectancy of ≤ 6 months, prior to commencement of systemic anticancer therapies with or without radiotherapy for gastrointestinal or lung cancer (newly diagnosed or relapsed or progressive disease, curative or palliative intent) at 5 hospitals in Australia. Exclusion criteria: Patients with contraindication to enoxaparin, including conditions placing them at high risk	Enoxaparin 40 mg, subcutaneously daily for a minimum of 90 days (extended up to 180 days according to ongoing risk)	No thromboprophylaxis	Length of follow-up: 180 days ± 30 days Loss-to-follow-up: Intervention: NR However it was described that 41 (41%) patients discontinued treatment: patient choice (N=8, no reason (N=7), new contraindication (N=6), end of life care (N=6), CRNM bleeding (N=6), thromboembolism (N=3), major bleeding (N=1), other (N=4)) and 2 (2%) patients did not receive intervention. Control: 0 (0%) Reasons: NA Incomplete outcome data: Intervention: NR Control: NR	**All VTE** *DVT must be confirmed by ultrasonography, venography or magnetic resonance angiography (cerebral events). PE must be confirmed by spiral CT, CT pulmonary angiography (CTPA) or lung ventilation/ perfusion scan.* I: 7/100 (7%) C: 22/100 (22%) aHR (95%CI): 0.28 (0.12-0.65) P = NR **ATE** *ATE must be confirmed by relevant radiologic imaging, or specifically for myocardial infarct (MI) must meet criteria outlined in the universal definition of MI considering biomarker changes, ischemic symptoms, ECG changes, cardiac imaging abnormalities, and cardiac death.* I: 1/100 (1%) C: 2/100 (2%)	ITT analysis was performed Fibrinogen and d-dimer levels were used to identify patients with high risk on thromboembolism. In total 200 high-risk patients were randomized to receive either enoxaparin or no thromboprophylaxis. Other patients (low risk, N=128) were assigned to the observational group. These data were not taken into account in our literature analysis. Of the 100 patients in the intervention group, N=41 discontinued treatment

		of bleeding or requiring therapeutic anticoagulation. <u>N total at baseline</u>: Intervention: 100 Control: 100 <u>Important prognostic factors[2]</u>: *Age (median years (range))* I: 67 (30-87) C: 66 (31-85) *Sex:* I: 62% M C: 55% M *Metastatic disease (n (%)):* I: 52 (52%) C: 44 (44%) *Previous thromboembolism (n (%))* I: 5 (5%) C: 7 (7%) Groups comparable at baseline? Yes				aHR (95%CI): 0.78 (0.05-13.20) P = NR **All thromboembolism** *Defined as DVT, PE and ATE.* I: 8/100 (8%) * C: 23/100 (23%) HR (95%CI): 0.30 (0.13-0.68) P = 0.005 * 6/8 thromboembolic events occurred without active enoxaparin therapy. **Major bleeding** *Defined as clinically overt bleeding meeting at least one of the following criteria: fatal bleeding; symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; bleeding causing a fall in haemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells. Clinically overt was defined as new onset visible bleeding or signs and symptoms suggestive of bleeding which in the absence of visible bleeding were confirmed by relevant imaging techniques.* I: 1/100 (1%) C: 2/100 (2%)	

						aHR (95%CI): 2.63 (0.23-29.71) P = NR **CRNMB** *Defined as bleeding not meeting criteria for major bleeding but that would be considered relevant and not trivial by a patient and physician.* I: 16/100 (16%) C: 9/100 (9%) aHR (95%CI): 0.68 (0.30-1.55) P = NR *one patient in the control group had both major bleeding and CRNMB. **Mortality** *Defined as 6 month all cause mortality* I: 13/100 (13%) C: 26/100 (26%) aHR (95%CI): 0.45 (0.23-0.87)) P = NR **Quality of life** *Not reported in this article yet.* **Treatment adherence** NR *****Adjusted for cancer diagnosis, cancer treatment, stage and hospital site.	

Risk of bias table for intervention studies (randomized controlled trials; based on Cochrane risk of bias tool and suggestions by the CLARITY Group at McMaster University)

5 **Research question:** What are the (un)desirable effects of thromboprophylaxis with Direct Oral Anticoagulants (DOAC), Low-Molecular-Weight Heparin (LMWH) or fondaparinux in adult ambulatory patients with malignancy in which systemic anticancer treatment was initiated, compared to placebo or standard of care?

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Alexander (2023)	**Definitely yes;** Reason: Randomization was performed using the randomization	**Definitely yes;** Reason: Randomization was performed blinded	**Definitely no;** Reason: Open-label trial (after randomization the	**No information**	**Probably yes;** Reason: Not all relevant outcomes are reported yet, but might	**Definitely yes**; Reason: No other problems noted:	**Some concerns** (major bleeding, VTE, mortality, CRNMB, any thromboembolism)

	module created by an independent statistician.	and in advance of patient recruitment.	study team, treating clinician and patient were unblinded to treatment allocation). TE and bleeding events were adjudicated by a committee unaware of randomisation.		be reported in other (new) articles.		**HIGH** (quality of life, discontinuation/ supplementation of oncological treatment, quality of dying and death)

Table of excluded studies

Excluded studies part I

Reference	Reason for exclusion
Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, Kuruvilla P, Hill D, Spadafora S, Marquis K, Trinkaus M, Tomiak A, Lee AYY, Gross PL, Lazo-Langner A, El-Maraghi R, Goss G, Le Gal G, Stewart D, Ramsay T, Rodger M, Witham D, Wells PS; AVERT Investigators. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. N Engl J Med. 2019 Feb 21;380(8):711-719. doi: 10.1056/NEJMoa1814468. Epub 2018 Dec 4. PMID: 30511879.	Included in Rutjes (2020)
Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, Streiff MB, Garcia DA, Liebman HA, Belani CP, O'Reilly EM, Patel JN, Yimer HA, Wildgoose P, Burton P, Vijapurkar U, Kaul S, Eikelboom J, McBane R, Bauer KA, Kuderer NM, Lyman GH; CASSINI Investigators. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. N Engl J Med. 2019 Feb 21;380(8):720-728. doi: 10.1056/NEJMoa1814630. PMID: 30786186	Included in Rutjes (2020)
Akl EA, Kahale LA, Ballout RA, Barba M, Yosuico VE, van Doormaal FF, Middeldorp S, Bryant A, Schünemann H. Parenteral anticoagulation in ambulatory patients with cancer. Cochrane Database Syst Rev. 2014 Dec 10;(12):CD006652. doi: 10.1002/14651858.CD006652.pub4. Update in: Cochrane Database Syst Rev. 2017 Sep 11;9:CD006652. PMID: 25491949.	Recent review available.
Bosch FTM, Mulder FI, Kamphuisen PW, Middeldorp S, Bossuyt PM, Büller HR, van Es N. Primary thromboprophylaxis in ambulatory cancer patients with a high Khorana score: a systematic review and meta-analysis. Blood Adv. 2020 Oct 27;4(20):5215-5225. doi: 10.1182/bloodadvances.2020003115. PMID: 33104795; PMCID: PMC7594395.	Included only studies in high-risk patients.
Agnelli G, Gussoni G, Bianchini C, Verso M, Mandalà M, Cavanna L, Barni S, Labianca R, Buzzi F, Scambia G, Passalacqua R, Ricci S, Gasparini G, Lorusso V, Bonizzoni E, Tonato M; PROTECHT Investigators. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. Lancet Oncol. 2009 Oct;10(10):943-9. doi: 10.1016/S1470-	Included in Rutjes (2020)

2045(09)70232-3. Epub 2009 Aug 31. PMID: 19726226.	
Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, Kuruvilla P, Hill D, Spadafora S, Marquis K, Trinkaus M, Tomiak A, Lee AYY, Gross PL, Lazo-Langner A, El-Maraghi R, Goss G, Le Gal G, Stewart D, Ramsay T, Rodger M, Witham D, Wells PS; AVERT Investigators. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. N Engl J Med. 2019 Feb 21;380(8):711-719. doi: 10.1056/NEJMoa1814468. Epub 2018 Dec 4. PMID: 30511879.	Included in Rutjes (2020)
Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, Streiff MB, Garcia DA, Liebman HA, Belani CP, O'Reilly EM, Patel JN, Yimer HA, Wildgoose P, Burton P, Vijapurkar U, Kaul S, Eikelboom J, McBane R, Bauer KA, Kuderer NM, Lyman GH; CASSINI Investigators. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. N Engl J Med. 2019 Feb 21;380(8):720-728. doi: 10.1056/NEJMoa1814630. PMID: 30786186	Included in Rutjes (2020)
Akl EA, Kahale LA, Ballout RA, Barba M, Yosuico VE, van Doormaal FF, Middeldorp S, Bryant A, Schünemann H. Parenteral anticoagulation in ambulatory patients with cancer. Cochrane Database Syst Rev. 2014 Dec 10;(12):CD006652. doi: 10.1002/14651858.CD006652.pub4. Update in: Cochrane Database Syst Rev. 2017 Sep 11;9:CD006652. PMID: 25491949.	Recent review available.
Bosch FTM, Mulder FI, Kamphuisen PW, Middeldorp S, Bossuyt PM, Büller HR, van Es N. Primary thromboprophylaxis in ambulatory cancer patients with a high Khorana score: a systematic review and meta-analysis. Blood Adv. 2020 Oct 27;4(20):5215-5225. doi: 10.1182/bloodadvances.2020003115. PMID: 33104795; PMCID: PMC7594395.	Included only studies in high-risk patients.

Studies excluded in Rutjes (2020)

Reference	Reason for exclusion
Campos-Cabrera G, Mendez-Garcia E, Campos-CabreraS, Campos-VillagomezJL, Campos-CabreraV. Rivaroxaban or aspirin as thromboprophylaxis in multiple myeloma. Blood 2018;132(Suppl 1):5068. [DOI: 10.1182/blood-2018-99-111579]	wrong comparison
Chahinian AP, Propert KJ, Ware JH, Zimmer B, Perry MC, Hirsh V, Skarin A, Kopel S, Holland JF, Comis RL, et al. A randomized trial of anticoagulation with warfarin and of alternating chemotherapy in extensive small-cell lung cancer by the Cancer and	wrong intervention

Leukemia Group B. J Clin Oncol. 1989 Aug;7(8):993-1002. doi: 10.1200/JCO.1989.7.8.993. PMID: 2547030.	
van Doormaal FF, Di Nisio M, Otten HM, Richel DJ, Prins M, Buller HR. Randomized trial of the effect of the low molecular weight heparin nadroparin on survival in patients with cancer. J Clin Oncol. 2011 May 20;29(15):2071-6. doi: 10.1200/JCO.2010.31.9293. Epub 2011 Apr 18. PMID: 21502549.	wrong intervention
Ek L, Gezelius E, Bergman B, Bendahl PO, Anderson H, Sundberg J, Wallberg M, Falkmer U, Verma S, Belting M; Swedish Lung Cancer Study Group (SLUSG). Randomized phase III trial of low-molecular-weight heparin enoxaparin in addition to standard treatment in small-cell lung cancer: the RASTEN trial. Ann Oncol. 2018 Feb 1;29(2):398-404. doi: 10.1093/annonc/mdx716. PMID: 29106448; PMCID: PMC5834130.	wrong intervention
Elit LM, Lee AY, Parpia S, Swystun LL, Liaw PC, Hoskins P, Julian DH, Julian JA, Levine MN. Dalteparin low molecular weight heparin (LMWH) in ovarian cancer: a phase II randomized study. Thromb Res. 2012 Dec;130(6):894-900. doi: 10.1016/j.thromres.2012.09.010. Epub 2012 Oct 7. PMID: 23046525.	wrong comparison
Greiner J, Schrappe M, Claviez A, Zimmermann M, Niemeyer C, Kolb R, Eberl W, Berthold F, Bergsträsser E, Gnekow A, Lassay E, Vorwerk P, Lauten M, Sauerbrey A, Rischewski J, Beilken A, Henze G, Korte W, Möricke A; THROMBOTECT Study Investigators. THROMBOTECT - a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents. Haematologica. 2019 Apr;104(4):756-765. doi: 10.3324/haematol.2018.194175. Epub 2018 Sep 27. PMID: 30262570; PMCID: PMC6442986.	wrong population
Haas SK, Freund M, Heigener D, HeilmannL, Kemkes- Matthes B, von TempelhoK GF, TOPIC Investigators. Lowmolecular- weight heparin versus placebo for the prevention of venous thromboembolism in metastatic breast cancer or stage III/IV lung cancer. Clinical and Applied Thrombosis Hemostasis 2012;18(2):159-65.	wrong intervention (TOPIC 1 and TOPIC 2), study terminated

Khorana AA, Francis CW, Kuderer NM, Carrier M, Ortel TL, Wun T, Rubens D, Hobbs S, Iyer R, Peterson D, Baran A, Kaproth-Joslin K, Lyman GH. Dalteparin thromboprophylaxis in cancer patients at high risk for venous thromboembolism: A randomized trial. Thromb Res. 2017 Mar;151:89-95. doi: 10.1016/j.thromres.2017.01.009. Epub 2017 Jan 26. PMID: 28139259.	study terminated
Klerk CP, Smorenburg SM, Otten HM, Lensing AW, Prins MH, Piovella F, Prandoni P, Bos MM, Richel DJ, van Tienhoven G, Büller HR. The effect of low molecular weight heparin on survival in patients with advanced malignancy. J Clin Oncol. 2005 Apr 1;23(10):2130-5. doi: 10.1200/JCO.2005.03.134. Epub 2005 Feb 7. PMID: 15699479.	wrong intervention
Larocca A, Cavallo F, Bringhen S, Di Raimondo F, Falanga A, Evangelista A, Cavalli M, Stanevsky A, Corradini P, Pezzatti S, Patriarca F, Cavo M, Peccatori J, Catalano L, Carella AM, Cafro AM, Siniscalchi A, Crippa C, Petrucci MT, Yehuda DB, Beggiato E, Di Toritto TC, Boccadoro M, Nagler A, Palumbo A. Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. Blood. 2012 Jan 26;119(4):933-9; quiz 1093. doi: 10.1182/blood-2011-03-344333. Epub 2011 Aug 11. PMID: 21835953.	wrong comparison
Lebeau B, Chastang C, Brechot JM, Capron F, Dautzenberg B, Delaisements C, Mornet M, Brun J, Hurdebourcq JP, Lemarie E. Subcutaneous heparin treatment increases survival in small cell lung cancer. "Petites Cellules" Group. Cancer. 1994 Jul 1;74(1):38-45. doi: 10.1002/1097-0142(19940701)74:1<38::aid-cncr2820740108>3.0.co;2-e. PMID: 8004580.	wrong intervention
Lecumberri R, López Vivanco G, Font A, González Billalabeitia E, Gúrpide A, Gómez Codina J, Isla D, Galán A, Bover I, Domine M, Vicente V, Rosell R, Rocha E. Adjuvant therapy with bemiparin in patients with limited-stage small cell lung cancer: results from the ABEL study. Thromb Res. 2013;132(6):666-70. doi: 10.1016/j.thromres.2013.09.026. Epub 2013 Sep 27. PMID: 24491267.	wrong intervention
Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanga A, Samosh M, Bramwell V, Pritchard KI, Stewart D, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. Lancet. 1994 Apr	wrong intervention

9;343(8902):886-9. doi: 10.1016/s0140-6736(94)90008-6. PMID: 7908358.	
Levine MN, Gu C, Liebman HA, Escalante CP, Solymoss S, Deitchman D, Ramirez L, Julian J. A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer. J Thromb Haemost. 2012 May;10(5):807-14. doi: 10.1111/j.1538-7836.2012.04693.x. PMID: 22409262.	wrong comparison, Phase II trial
Maraveyas A, Waters J, Roy R, Fyfe D, Propper D, Lofts F, Sgouros J, Gardiner E, Wedgwood K, Ettelaie C, Bozas G. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer. 2012 Jun;48(9):1283-92. doi: 10.1016/j.ejca.2011.10.017. Epub 2011 Nov 17. PMID: 22100906.	phase II trial, wrong intervention
Maurer LH, Herndon JE 2nd, Hollis DR, Aisner J, Carey RW, Skarin AT, Perry MC, Eaton WL, Zacharski LL, Hammond S, Green MR. Randomized trial of chemotherapy and radiation therapy with or without warfarin for limited-stage small-cell lung cancer: a Cancer and Leukemia Group B study. J Clin Oncol. 1997 Nov;15(11):3378-87. doi: 10.1200/JCO.1997.15.11.3378. PMID: 9363869.	wrong intervention
Meyer G, Besse B, Doubre H, Charles-Nelson A, Aquilanti S, Izadifar A, Azarian R, Monnet I, Lamour C, Descourt R, Oliviero G, Taillade L, Chouaid C, Giraud F, Falcoz PE, Revel MP, Westeel V, Dixmier A, Tredaniel J, Dehette S, Decroisette C, Prevost A, Pichon E, Fabre E, Soria JC, Friard S, Stern JB, Jabot L, Dennewald G, Pavy G, Petitpretz P, Tourani JM, Alifano M, Chatellier G, Girard P. Anti-tumour effect of low molecular weight heparin in localised lung cancer: a phase III clinical trial. Eur Respir J. 2018 Oct 4;52(4):1801220. doi: 10.1183/13993003.01220-2018. PMID: 30262574.	wrong intervention
Mitchell L, Andrew M, Hanna K, Abshire T, Halton J, Wu J, Anderson R, Cherrick I, Desai S, Mahoney D, McCusker P, Chait P, Abdolell M, de Veber G, Mikulis D. Trend to efficacy and safety using antithrombin concentrate in prevention of thrombosis in children receiving l-asparaginase for acute lymphoblastic leukemia. Results of the PAARKA study. Thromb Haemost. 2003 Aug;90(2):235-44. doi: 10.1160/TH02-11-0283. PMID: 12888870.	wrong intervention, wrong population, Phase II trial
Palumbo A, Cavo M, Bringhen S, Zamagni E, Romano A, Patriarca F, Rossi D, Gentilini F, Crippa C, Galli M, Nozzoli C, Ria R, Marasca R, Montefusco V, Baldini L, Elice F, Callea V, Pulini S, Carella AM, Zambello R,	wrong comparison

Benevolo G, Magarotto V, Tacchetti P, Pescosta N, Cellini C, Polloni C, Evangelista A, Caravita T, Morabito F, Offidani M, Tosi P, Boccadoro M. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. J Clin Oncol. 2011 Mar 10;29(8):986-93. doi: 10.1200/JCO.2010.31.6844. Epub 2011 Jan 31. PMID: 21282540.	
Pelzer U, Opitz B, Deutschinoff G, Stauch M, Reitzig PC, Hahnfeld S, Müller L, Grunewald M, Stieler JM, Sinn M, Denecke T, Bischoff S, Oettle H, Dörken B, Riess H. Efficacy of Prophylactic Low-Molecular Weight Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From the CONKO-004 Trial. J Clin Oncol. 2015 Jun 20;33(18):2028-34. doi: 10.1200/JCO.2014.55.1481. Epub 2015 May 18. PMID: 25987694.	wrong intervention
Zacharski LR, Henderson WG, Rickles FR, Forman WB, Cornell CJ Jr, Forcier RJ, Edwards R, Headley E, Kim SH, O'Donnell JR, O'Dell R, Tornyos K, Kwaan HC. Effect of warfarin on survival in small cell carcinoma of the lung. Veterans Administration Study No. 75. JAMA. 1981 Feb 27;245(8):831-5. PMID: 6257941.	wrong intervention
Zwicker JI, Liebman HA, Bauer KA, Caughey T, Campigotto F, Rosovsky R, Mantha S, Kessler CM, Eneman J, Raghavan V, Lenz HJ, Bullock A, Buchbinder E, Neuberg D, Furie B. Prediction and prevention of thromboembolic events with enoxaparin in cancer patients with elevated tissue factor-bearing microparticles: a randomized-controlled phase II trial (the Microtec study). Br J Haematol. 2013 Feb;160(4):530-7. doi: 10.1111/bjh.12163. Epub 2012 Dec 13. PMID: 23240761; PMCID: PMC3609903.	phase II trial, wrong intervention
Vadhan-Raj S, Zhou_X, Varadhachary_GR, Milind_J, Fogelman_D, ShroK_R, et al. Randomized controlled trial of dalteparin for primary thromboprophylaxis for venous thromboembolism (VTE) in patients with advanced pancreatic cancer (APC): risk factors predictive of VTE. 55th Annual Meeting of the American Society of Hematology; 2013 Dec 7-10; New Orleans, LA.	abstract

Literature search strategy

Zoekverantwoording

Algemene informatie

Richtlijn: Cluster antitrombotische beleid

Uitgangsvraag: UV3 Moeten poliklinische patiënten met kanker tijdens systemische kankerbehandeling farmacologische tromboseprofylaxe krijgen als primaire preventie voor veneuze tromboembolie?	
Database(s): Ovid/Medline, Embase	Datum: 4-7-2023 en 14-9-2023
Periode: nvt	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp en Esther van der Bijl	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: **14-9-2023** Na de selectie is geconstateerd dat niet alle relevante literatuur wordt gevonden. Naar aanleiding van gevonden evidence in 2020 wordt gevraagd om een update van de zoekstrategie, waarin de setting ambulante patiënten achterwege wordt gelaten en gezocht wordt vanaf 2020. Het resultaat wordt ontdubbeld t.o.v. het eerder gevonden resultaat op 4 juli. **4-7-2023** Voor deze vraag is gezocht met de volgende concepten: Systeemtherapie EN farmacologische tromboseprofylaxe EN ambulante patiënten Er is geen onderscheid gemaakt tussen volwassenen en kinderen. De drie sleutelartikelen worden gevonden.	

Zoekopbrengst 12-10-2023	**EMBASE vanaf 2023**	**OVID/MEDLINE vanaf 2020**	**Ontdubbeld t.o.v. Rayyan 14-9-2023**
SRs	81	24	7
RCTs	61	37	1
Observationele studies			
Totaal			819
Zoekopbrengst 14-9-2023	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld t.o.v. Rayyan 4-7-2023**
SRs	513	24	485
RCTs	338	35	326
Observationele studies			
Totaal	851	59	811

Zoekopbrengst 4-7-2023

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	67	21	62
RCTs	38	22	42
Observationele studies			
Totaal	105	43	104

Zoekstrategie

Embase 14-9-2023

#16	#12 AND [2020-2023]py RCT	338
#15	#11 AND [2020-2023]py SR	513
#14	#4 AND #13 sleutelartikelen gevonden	3
#13	#11 OR #12	2215
#12	#8 AND #10 NOT #11	988
#11	#8 AND #9	1227
#10	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	2099619
#9	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	961476
#8	#7 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	15307
#7	#5 AND #6	20071
#6	'low molecular weight heparin'/exp OR 'dalteparin'/exp OR 'enoxaparin'/exp OR 'nadroparin'/exp OR 'tinzaparin'/exp OR 'fondaparinux'/exp OR 'apixaban'/exp OR 'dabigatran'/exp OR 'rivaroxaban'/exp OR 'bm 2123':ti,ab,kw OR 'bm2123':ti,ab,kw OR 'choay':ti,ab,kw OR 'depolymerized heparin':ti,ab,kw OR 'ebpm	118112

	1':ti,ab,kw OR 'ebpm 2':ti,ab,kw OR 'ebpm 3':ti,ab,kw OR 'ebpm1':ti,ab,kw OR 'ebpm2':ti,ab,kw OR 'ebpm3':ti,ab,kw OR 'ff 1034':ti,ab,kw OR 'ff1034':ti,ab,kw OR 'fr 860':ti,ab,kw OR 'low molecular heparin':ti,ab,kw OR 'low molecular weight heparin':ti,ab,kw OR 'nm heparin':ti,ab,kw OR 'pk 007':ti,ab,kw OR 'sandoz 5100':ti,ab,kw OR 'sandoz 6700':ti,ab,kw OR 'traxyparine':ti,ab,kw OR lmwh:ti,ab,kw OR 'assubex':ti,ab,kw OR 'kriva':ti,ab,kw OR 'naxat':ti,ab,kw OR 'rivaro':ti,ab,kw OR 'rivarolto':ti,ab,kw OR 'rivaroxaban':ti,ab,kw OR 'rivaxa':ti,ab,kw OR 'throsaben':ti,ab,kw OR 'xanirva':ti,ab,kw OR 'xarelto':ti,ab,kw OR 'xerdoxo':ti,ab,kw OR 'xindus':ti,ab,kw OR 'bibr 953':ti,ab,kw OR 'bibr953':ti,ab,kw OR 'dabigatran':ti,ab,kw OR 'aboxoma':ti,ab,kw OR 'apixaban':ti,ab,kw OR 'apixaben':ti,ab,kw OR 'bms 562247':ti,ab,kw OR 'bms562247':ti,ab,kw OR 'bms562247 01':ti,ab,kw OR 'eliques':ti,ab,kw OR 'eliquis':ti,ab,kw OR 'lunast':ti,ab,kw OR 'pf 0465257':ti,ab,kw OR 'pf0465257':ti,ab,kw OR 'tah 3311':ti,ab,kw OR 'tah3311':ti,ab,kw OR 'arixtra':ti,ab,kw OR 'fondaparin*':ti,ab,kw OR 'gsk 576428':ti,ab,kw OR 'gsk576428':ti,ab,kw OR 'ic 851589':ti,ab,kw OR 'ic851589':ti,ab,kw OR 'org 31540':ti,ab,kw OR 'org31540':ti,ab,kw OR 'quixidar':ti,ab,kw OR 'sr 90107':ti,ab,kw OR 'sr 90107a':ti,ab,kw OR 'sr90107':ti,ab,kw OR 'sr90107a':ti,ab,kw OR 'xantidar':ti,ab,kw OR 'innohep':ti,ab,kw OR 'lhn1':ti,ab,kw OR 'logiparin':ti,ab,kw OR 'tinzaparin':ti,ab,kw OR 'dalteparin':ti,ab,kw OR 'fragmin':ti,ab,kw OR 'fragmine':ti,ab,kw OR 'k 2165':ti,ab,kw OR 'k2165':ti,ab,kw OR 'kabi 2165':ti,ab,kw OR 'low liquemin':ti,ab,kw OR 'arovi':ti,ab,kw OR 'clexan':ti,ab,kw OR 'clexane':ti,ab,kw OR 'colevance':ti,ab,kw OR 'crusia':ti,ab,kw OR 'decipar':ti,ab,kw OR 'enoxaparin':ti,ab,kw OR 'ghemaxan':ti,ab,kw OR 'hepaxane':ti,ab,kw OR 'inhixa':ti,ab,kw OR 'klexane':ti,ab,kw OR 'ledraxen':ti,ab,kw OR 'losima':ti,ab,kw OR 'lovenox':ti,ab,kw OR 'neoparin':ti,ab,kw OR 'percolozin':ti,ab,kw OR 'pk 10169':ti,ab,kw OR 'pk10169':ti,ab,kw OR 'qualiop klinik':ti,ab,kw OR 'rovinadil':ti,ab,kw OR 'rp 54563':ti,ab,kw OR 'rp54563':ti,ab,kw OR 'thorinane':ti,ab,kw OR 'cy 216':ti,ab,kw OR 'cy 216d':ti,ab,kw OR 'cy216':ti,ab,kw OR 'cy216d':ti,ab,kw OR 'fraxiparin':ti,ab,kw OR 'fraxodi':ti,ab,kw OR 'nadroparin*':ti,ab,kw OR 'seledie':ti,ab,kw OR 'seleparina':ti,ab,kw OR 'seleparine':ti,ab,kw OR 'tedegliparin':ti,ab,kw	
#5	'systemic therapy'/exp AND ('neoplasm'/exp OR neoplas*:ti,ab,kw OR carcinom*:ti,ab,kw OR cancer*:ti,ab,kw OR malignan*:ti,ab,kw OR tumor*:ti,ab,kw OR tumour*:ti,ab,kw OR metasta*) OR 'cancer immunotherapy'/exp OR 'cancer hormone therapy'/exp OR 'molecularly targeted therapy'/exp OR 'multimodality cancer therapy'/exp OR 'chemotherapy'/exp OR 'antineoplastic agent'/exp OR 'checkpoint inhibitor therapy'/exp OR 'protein kinase inhibitor'/exp OR ((((hormon* OR endocrin* OR 'combined modalit*' OR multimodal* OR 'multiple modalit*' OR target* OR immun* OR systemic* OR checkpoint OR 'check point') NEAR/3 (therap* OR treat*)):ti,ab,kw) AND ('neoplasm'/exp OR neoplas*:ti,ab,kw OR carcinom*:ti,ab,kw OR cancer*:ti,ab,kw OR malignan*:ti,ab,kw OR	3982517

	tumor*:ti,ab,kw OR tumour*:ti,ab,kw OR metasta*:ti,ab,kw)) OR 'biologic response modifier therapy':ti,ab,kw OR 'biological response modifier therapy':ti,ab,kw OR 'chemoradiotherapy'/exp OR 'chemoradi*':ti,ab,kw OR 'radiochemo*':ti,ab,kw OR chemotherap*:ti,ab,kw OR ((antineoplastic NEAR/3 (drug* OR agent*)):ti,ab,kw) OR 'protein kinase inhibitor*':ti,ab,kw	
#4	#1 OR #2 OR #3 sleutelartikelen	3
#3	'primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy' AND [2020]/py AND rutjes	1
#2	'rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer' AND khorana	1
#1	'apixaban to prevent venous thromboembolism in patients with cancer'	1

Zoekstrategie

Embase 4-7-2023

#15	#4 AND #14 sleutelartikelen gevonden	3
#14	#12 OR #13	105
#13	#9 AND #11 NOT #12 RCT	38
#12	#9 AND #10 SR	67
#11	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	2070573
#10	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	940686
#9	#8 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	217
#8	#5 AND #6 AND #7	437
#7	'outpatient department'/exp OR 'ambulatory care'/exp OR 'outpatient'/exp OR 'outpatient care'/exp OR ambulator*:ti,ab,kw OR dispensar*:ti,ab,kw OR extramural:ti,ab,kw OR oupatient*:ti,ab,kw	462561

	OR 'out patient':ti,ab,kw OR 'outward patient*':ti,ab,kw OR policlinic*:ti,ab,kw OR polyclinic*:ti,ab,kw	
#6	'low molecular weight heparin'/exp OR 'dalteparin'/exp OR 'enoxaparin'/exp OR 'nadroparin'/exp OR 'tinzaparin'/exp OR 'fondaparinux'/exp OR 'apixaban'/exp OR 'dabigatran'/exp OR 'rivaroxaban'/exp OR 'bm 2123':ti,ab,kw OR 'bm2123':ti,ab,kw OR 'choay':ti,ab,kw OR 'depolymerized heparin':ti,ab,kw OR 'ebpm 1':ti,ab,kw OR 'ebpm 2':ti,ab,kw OR 'ebpm 3':ti,ab,kw OR 'ebpm1':ti,ab,kw OR 'ebpm2':ti,ab,kw OR 'ebpm3':ti,ab,kw OR 'ff 1034':ti,ab,kw OR 'ff1034':ti,ab,kw OR 'fr 860':ti,ab,kw OR 'low molecular heparin':ti,ab,kw OR 'low molecular weight heparin':ti,ab,kw OR 'nm heparin':ti,ab,kw OR 'pk 007':ti,ab,kw OR 'sandoz 5100':ti,ab,kw OR 'sandoz 6700':ti,ab,kw OR 'traxyparine':ti,ab,kw OR lmwh:ti,ab,kw OR 'assubex':ti,ab,kw OR 'kriva':ti,ab,kw OR 'naxat':ti,ab,kw OR 'rivaro':ti,ab,kw OR 'rivarolto':ti,ab,kw OR 'rivaroxaban':ti,ab,kw OR 'rivaxa':ti,ab,kw OR 'throsaben':ti,ab,kw OR 'xanirva':ti,ab,kw OR 'xarelto':ti,ab,kw OR 'xerdoxo':ti,ab,kw OR 'xindus':ti,ab,kw OR 'bibr 953':ti,ab,kw OR 'bibr953':ti,ab,kw OR 'dabigatran':ti,ab,kw OR 'aboxoma':ti,ab,kw OR 'apixaban':ti,ab,kw OR 'apixaben':ti,ab,kw OR 'bms 562247':ti,ab,kw OR 'bms562247':ti,ab,kw OR 'bms562247 01':ti,ab,kw OR 'eliques':ti,ab,kw OR 'eliquis':ti,ab,kw OR 'lunast':ti,ab,kw OR 'pf 0465257':ti,ab,kw OR 'pf0465257':ti,ab,kw OR 'tah 3311':ti,ab,kw OR 'tah3311':ti,ab,kw OR 'arixtra':ti,ab,kw OR 'fondaparin*':ti,ab,kw OR 'gsk 576428':ti,ab,kw OR 'gsk576428':ti,ab,kw OR 'ic 851589':ti,ab,kw OR 'ic851589':ti,ab,kw OR 'org 31540':ti,ab,kw OR 'org31540':ti,ab,kw OR 'quixidar':ti,ab,kw OR 'sr 90107':ti,ab,kw OR 'sr 90107a':ti,ab,kw OR 'sr90107':ti,ab,kw OR 'sr90107a':ti,ab,kw OR 'xantidar':ti,ab,kw OR 'innohep':ti,ab,kw OR 'lhn1':ti,ab,kw OR 'logiparin':ti,ab,kw OR 'tinzaparin':ti,ab,kw OR 'dalteparin':ti,ab,kw OR 'fragmin':ti,ab,kw OR 'fragmine':ti,ab,kw OR 'k 2165':ti,ab,kw OR 'k2165':ti,ab,kw OR 'kabi 2165':ti,ab,kw OR 'low liquemin':ti,ab,kw OR 'arovi':ti,ab,kw OR 'clexan':ti,ab,kw OR 'clexane':ti,ab,kw OR 'colevance':ti,ab,kw OR 'crusia':ti,ab,kw OR 'decipar':ti,ab,kw OR 'enoxaparin':ti,ab,kw OR 'ghemaxan':ti,ab,kw OR 'hepaxane':ti,ab,kw OR 'inhixa':ti,ab,kw OR 'klexane':ti,ab,kw OR 'ledraxen':ti,ab,kw OR 'losima':ti,ab,kw OR 'lovenox':ti,ab,kw OR 'neoparin':ti,ab,kw OR 'percolozin':ti,ab,kw OR 'pk 10169':ti,ab,kw OR 'pk10169':ti,ab,kw OR 'qualiop klinik':ti,ab,kw OR 'rovinadil':ti,ab,kw OR 'rp 54563':ti,ab,kw OR 'rp54563':ti,ab,kw OR 'thorinane':ti,ab,kw OR 'cy 216':ti,ab,kw OR 'cy 216d':ti,ab,kw OR 'cy216':ti,ab,kw OR 'cy216d':ti,ab,kw OR 'fraxiparin':ti,ab,kw OR 'fraxodi':ti,ab,kw OR 'nadroparin*':ti,ab,kw OR 'seledie':ti,ab,kw OR 'seleparina':ti,ab,kw OR 'seleparine':ti,ab,kw OR 'tedegliparin':ti,ab,kw	116390
#5	'systemic therapy'/exp AND ('neoplasm'/exp OR neoplas*:ti,ab,kw OR carcinom*:ti,ab,kw OR cancer*:ti,ab,kw OR malignan*:ti,ab,kw OR tumor*:ti,ab,kw OR tumour*:ti,ab,kw OR metasta*) OR 'cancer immunotherapy'/exp OR 'cancer hormone therapy'/exp OR 'molecularly targeted therapy'/exp OR 'multimodality cancer	3912136

	therapy'/exp OR 'chemotherapy'/exp OR 'antineoplastic agent'/exp OR 'checkpoint inhibitor therapy'/exp OR 'protein kinase inhibitor'/exp OR ((((hormon* OR endocrin* OR 'combined modalit*' OR multimodal* OR 'multiple modalit*' OR target* OR immun* OR systemic* OR checkpoint OR 'check point') NEAR/3 (therap* OR treat*)):ti,ab,kw) AND ('neoplasm'/exp OR neoplas*:ti,ab,kw OR carcinom*:ti,ab,kw OR cancer*:ti,ab,kw OR malignan*:ti,ab,kw OR tumor*:ti,ab,kw OR tumour*:ti,ab,kw OR metasta*:ti,ab,kw)) OR 'biologic response modifier therapy':ti,ab,kw OR 'biological response modifier therapy':ti,ab,kw OR 'chemoradiotherapy'/exp OR 'chemoradi*':ti,ab,kw OR 'radiochemo*':ti,ab,kw OR chemotherap*:ti,ab,kw OR ((antineoplastic NEAR/3 (drug* OR agent*)):ti,ab,kw) OR 'protein kinase inhibitor*':ti,ab,kw	
#4	#1 OR #2 OR #3 sleutelartikelen	3
#3	'primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy' AND [2020]/py AND rutjes	1
#2	'rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer' AND khorana	1
#1	'apixaban to prevent venous thromboembolism in patients with cancer'	1

Zoekstrategie
Ovid/Medline 14-9-2023

#	Searches	Results
11	limit 8 to yr="2020 - 2024" RCT	35
10	limit 7 to yr="2020 - 2024" SR	24
9	7 or 8	264
8	4 and 6 (not 7)	180
7	4 and 5	84
6	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1644900
5	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data	693090

	extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	
4	3 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	1165
3	1 and 2	1335
2	exp Heparin, Low-Molecular-Weight/ or Dalteparin/ or Enoxaparin/ or Nadroparin/ or Tinzaparin/ or Dabigatran/ or Rivaroxaban/ or bm 2123.ti,ab,kf. or bm2123.ti,ab,kf. or choay.ti,ab,kf. or depolymerized heparin.ti,ab,kf. or ebpm 1.ti,ab,kf. or ebpm 2.ti,ab,kf. or ebpm 3.ti,ab,kf. or ebpm1.ti,ab,kf. or ebpm2.ti,ab,kf. or ebpm3.ti,ab,kf. or ff 1034.ti,ab,kf. or ff1034.ti,ab,kf. or fr 860.ti,ab,kf. or low molecular heparin.ti,ab,kf. or low molecular weight heparin.ti,ab,kf. or nm heparin.ti,ab,kf. or "pk 007".ti,ab,kf. or sandoz 5100.ti,ab,kf. or sandoz 6700.ti,ab,kf. or traxyparine.ti,ab,kf. or lmwh.ti,ab,kf. or assubex.ti,ab,kf. or kriva.ti,ab,kf. or naxat.ti,ab,kf. or rivaro.ti,ab,kf. or rivarolto.ti,ab,kf. or rivaroxaban.ti,ab,kf. or rivaxa.ti,ab,kf. or throsaben.ti,ab,kf. or xanirva.ti,ab,kf. or xarelto.ti,ab,kf. or xerdoxo.ti,ab,kf. or xindus.ti,ab,kf. or bibr 953.ti,ab,kf. or bibr953.ti,ab,kf. or dabigatran.ti,ab,kf. or aboxoma.ti,ab,kf. or apixaban.ti,ab,kf. or apixaben.ti,ab,kf. or bms 562247.ti,ab,kf. or bms562247.ti,ab,kf. or "bms562247 01".ti,ab,kf. or eliques.ti,ab,kf. or eliquis.ti,ab,kf. or lunast.ti,ab,kf. or "pf 0465257".ti,ab,kf. or pf0465257.ti,ab,kf. or tah 3311.ti,ab,kf. or tah3311.ti,ab,kf. or arixtra.ti,ab,kf. or fondaparin*.ti,ab,kf. or gsk 576428.ti,ab,kf. or gsk576428.ti,ab,kf. or ic 851589.ti,ab,kf. or ic851589.ti,ab,kf. or org 31540.ti,ab,kf. or org31540.ti,ab,kf. or quixidar.ti,ab,kf. or sr 90107.ti,ab,kf. or sr 90107a.ti,ab,kf. or sr90107.ti,ab,kf. or sr90107a.ti,ab,kf. or xantidar.ti,ab,kf. or innohep.ti,ab,kf. or lhn1.ti,ab,kf. or logiparin.ti,ab,kf. or tinzaparin.ti,ab,kf. or dalteparin.ti,ab,kf. or fragmin.ti,ab,kf. or fragmine.ti,ab,kf. or k 2165.ti,ab,kf. or k2165.ti,ab,kf. or kabi 2165.ti,ab,kf. or low liquemin.ti,ab,kf. or arovi.ti,ab,kf. or clexan.ti,ab,kf. or clexane.ti,ab,kf. or colevance.ti,ab,kf. or crusia.ti,ab,kf. or decipar.ti,ab,kf. or enoxaparin.ti,ab,kf. or ghemaxan.ti,ab,kf. or	34414

	hepaxane.ti,ab,kf. or inhixa.ti,ab,kf. or klexane.ti,ab,kf. or ledraxen.ti,ab,kf. or losima.ti,ab,kf. or lovenox.ti,ab,kf. or neoparin.ti,ab,kf. or percolozin.ti,ab,kf. or pk 10169.ti,ab,kf. or pk10169.ti,ab,kf. or qualiop klinik.ti,ab,kf. or rovinadil.ti,ab,kf. or rp 54563.ti,ab,kf. or rp54563.ti,ab,kf. or thorinane.ti,ab,kf. or cy 216.ti,ab,kf. or cy 216d.ti,ab,kf. or cy216.ti,ab,kf. or cy216d.ti,ab,kf. or fraxiparin.ti,ab,kf. or fraxodi.ti,ab,kf. or nadroparin*.ti,ab,kf. or seledie.ti,ab,kf. or seleparina.ti,ab,kf. or seleparine.ti,ab,kf. or tedegliparin.ti,ab,kf.	
1	Chemoradiotherapy/ or Chemotherapy, Adjuvant/ or Consolidation Chemotherapy/ or Electrochemotherapy/ or Induction Chemotherapy/ or Maintenance Chemotherapy/ or Molecular Targeted Therapy/ or Orthomolecular Therapy/ or Photochemotherapy/ or (Immunotherapy/ and (exp Neoplasms/ or (neoplas* or carcinom* or cancer* or malignan* or tumor* or tumour* or metasta*).ti,ab,kf.)) or exp Antineoplastic Agents/ or Immune Checkpoint Inhibitors/ or Protein Kinase Inhibitors/ or (((hormon* or endocrin* or combined modalit* or multimodal* or multiple modalit* or target* or immun* or systemic* or checkpoint or "check point") adj3 (therap* or treat*)).ti,ab,kf. and (exp Neoplasms/ or neoplas*.ti,ab,kf. or carcinom*.ti,ab,kf. or cancer*.ti,ab,kf. or malignan*.ti,ab,kf. or tumor*.ti,ab,kf. or tumour*.ti,ab,kf. or metasta*.ti,ab,kf.)) or biologic response modifier therapy.ti,ab,kf. or biological response modifier therapy.ti,ab,kf. or chemoradi*.ti,ab,kf. or radiochemo*.ti,ab,kf. or chemotherap*.ti,ab,kf. or (antineoplastic adj3 (drug* or agent*)).ti,ab,kf. or protein kinase inhibitor*.ti,ab,kf.	1871870

Zoekstrategie

Ovid/Medline 4-7-2023

#	Searches	Results
11	9 or 10	43
10	6 and 8 not 9 RCT	22
9	6 and 7 SR	21
8	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1625962

7	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	678494
6	5 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	75
5	3 and 4	81
4	Ambulatory Care/ or exp Outpatient Clinics, Hospital/ or Ambulatory Care Facilities/ or ambulator*.ti,ab,kf. or dispensar*.ti,ab,kf. or extramural.ti,ab,kf. or oupatient*.ti,ab,kf. or out patient.ti,ab,kf. or outward patient*.ti,ab,kf. or policlinic*.ti,ab,kf. or polyclinic*.ti,ab,kf.	179576
3	1 and 2	1327
2	exp Heparin, Low-Molecular-Weight/ or Dalteparin/ or Enoxaparin/ or Nadroparin/ or Tinzaparin/ or Dabigatran/ or Rivaroxaban/ or bm 2123.ti,ab,kf. or bm2123.ti,ab,kf. or choay.ti,ab,kf. or depolymerized heparin.ti,ab,kf. or ebpm 1.ti,ab,kf. or ebpm 2.ti,ab,kf. or ebpm 3.ti,ab,kf. or ebpm1.ti,ab,kf. or ebpm2.ti,ab,kf. or ebpm3.ti,ab,kf. or ff 1034.ti,ab,kf. or ff1034.ti,ab,kf. or fr 860.ti,ab,kf. or low molecular heparin.ti,ab,kf. or low molecular weight heparin.ti,ab,kf. or nm heparin.ti,ab,kf. or "pk 007".ti,ab,kf. or sandoz 5100.ti,ab,kf. or sandoz 6700.ti,ab,kf. or traxyparine.ti,ab,kf. or lmwh.ti,ab,kf. or assubex.ti,ab,kf. or kriva.ti,ab,kf. or naxat.ti,ab,kf. or rivaro.ti,ab,kf. or rivarolto.ti,ab,kf. or rivaroxaban.ti,ab,kf. or rivaxa.ti,ab,kf. or throsaben.ti,ab,kf. or xanirva.ti,ab,kf. or xarelto.ti,ab,kf. or xerdoxo.ti,ab,kf. or xindus.ti,ab,kf. or bibr 953.ti,ab,kf. or bibr953.ti,ab,kf. or dabigatran.ti,ab,kf. or aboxoma.ti,ab,kf. or apixaban.ti,ab,kf. or apixaben.ti,ab,kf. or bms	34104

	562247.ti,ab,kf. or bms562247.ti,ab,kf. or "bms562247 01".ti,ab,kf. or eliques.ti,ab,kf. or eliquis.ti,ab,kf. or lunast.ti,ab,kf. or "pf 0465257".ti,ab,kf. or pf0465257.ti,ab,kf. or tah 3311.ti,ab,kf. or tah3311.ti,ab,kf. or arixtra.ti,ab,kf. or fondaparin*.ti,ab,kf. or gsk 576428.ti,ab,kf. or gsk576428.ti,ab,kf. or ic 851589.ti,ab,kf. or ic851589.ti,ab,kf. or org 31540.ti,ab,kf. or org31540.ti,ab,kf. or quixidar.ti,ab,kf. or sr 90107.ti,ab,kf. or sr 90107a.ti,ab,kf. or sr90107.ti,ab,kf. or sr90107a.ti,ab,kf. or xantidar.ti,ab,kf. or innohep.ti,ab,kf. or lhn1.ti,ab,kf. or logiparin.ti,ab,kf. or tinzaparin.ti,ab,kf. or dalteparin.ti,ab,kf. or fragmin.ti,ab,kf. or fragmine.ti,ab,kf. or k 2165.ti,ab,kf. or k2165.ti,ab,kf. or kabi 2165.ti,ab,kf. or low liquemin.ti,ab,kf. or arovi.ti,ab,kf. or clexan.ti,ab,kf. or clexane.ti,ab,kf. or colevance.ti,ab,kf. or crusia.ti,ab,kf. or decipar.ti,ab,kf. or enoxaparin.ti,ab,kf. or ghemaxan.ti,ab,kf. or hepaxane.ti,ab,kf. or inhixa.ti,ab,kf. or klexane.ti,ab,kf. or ledraxen.ti,ab,kf. or losima.ti,ab,kf. or lovenox.ti,ab,kf. or neoparin.ti,ab,kf. or percolozin.ti,ab,kf. or pk 10169.ti,ab,kf. or pk10169.ti,ab,kf. or qualiop klinik.ti,ab,kf. or rovinadil.ti,ab,kf. or rp 54563.ti,ab,kf. or rp54563.ti,ab,kf. or thorinane.ti,ab,kf. or cy 216.ti,ab,kf. or cy 216d.ti,ab,kf. or cy216.ti,ab,kf. or cy216d.ti,ab,kf. or fraxiparin.ti,ab,kf. or fraxodi.ti,ab,kf. or nadroparin*.ti,ab,kf. or seledie.ti,ab,kf. or seleparina.ti,ab,kf. or seleparine.ti,ab,kf. or tedegliparin.ti,ab,kf.	
1	Chemoradiotherapy/ or Chemotherapy, Adjuvant/ or Consolidation Chemotherapy/ or Electrochemotherapy/ or Induction Chemotherapy/ or Maintenance Chemotherapy/ or Molecular Targeted Therapy/ or Orthomolecular Therapy/ or Photochemotherapy/ or (Immunotherapy/ and (exp Neoplasms/ or (neoplas* or carcinom* or cancer* or malignan* or tumor* or tumour* or metasta*).ti,ab,kf.)) or exp Antineoplastic Agents/ or Immune Checkpoint Inhibitors/ or Protein Kinase Inhibitors/ or (((hormon* or endocrin* or combined modalit* or multimodal* or multiple modalit* or target* or immun* or systemic* or checkpoint or "check point") adj3 (therap* or treat*)).ti,ab,kf. and (exp Neoplasms/ or neoplas*.ti,ab,kf. or carcinom*.ti,ab,kf. or cancer*.ti,ab,kf. or malignan*.ti,ab,kf. or tumor*.ti,ab,kf. or tumour*.ti,ab,kf. or metasta*.ti,ab,kf.)) or biologic response modifier therapy.ti,ab,kf. or biological response modifier therapy.ti,ab,kf. or chemoradi*.ti,ab,kf. or	1856533

	radiochemo*.ti,ab,kf. or chemotherap*.ti,ab,kf. or (antineoplastic adj3 (drug* or agent*)).ti,ab,kf. or protein kinase inhibitor*.ti,ab,kf.	

5

Module 4 Tromboseprofylaxe kinderen met maligniteit

Autorisatie en geldigheid

Autorisatiedatum:	*pending*
Eerstvolgende beoordeling actualiteit	volgende cyclus binnen het cluster Antitrombotisch beleid
Geautoriseerd door:	*pending*
Belangrijkste wijzigingen t.o.v. vorige versie:	In de nieuwe module worden met name aanbevelingen gegeven over tromboseprofylaxe bij alle kinderen met een maligniteit. 'Geef niet routinematig tromboseprofylaxe' is gewijzigd in 'Overweeg tromboseprofylaxe in specifieke gevallen (zie aanbevelingen voor de specificaties).
Herbevestiging:	n.v.t.
Regiehouder:	Nederlandse Internisten Vereniging

Vervangt:
https://richtlijnendatabase.nl/richtlijn/antitrombotisch_beleid/preventie_trombose_neonaten_kinderen_tot_18/kinderen_met_een_maligniteit.html

Uitgangsvraag
In hoeverre dient tromboseprofylaxe gegeven te worden bij (opgenomen) kinderen met een maligniteit?

Introduction
Children with cancer have an increased risk of developing thrombo-embolism because of the underlying disease and/or treatment, with prevalence ranging from 16 to 40% (Barg, 2020). Numerous risk factors for VTE in pediatric cancer patients have been identified, including cancer type, chemotherapy and central venous catheters. Children with lymphoma or acute lymphoblastic leukemia have a much higher risk than children with a solid tumor or brain tumor. Medication such as asparaginase and steroids increase the risk of thrombosis. The central venous catheter leads to an increased risk of thrombosis. Current guidelines do not advice standard thrombosis prophylaxis to children with cancer. The hypothesis is that thrombosis prophylaxis could be used in high-risk groups (teenagers, type of cancer, CVL, type of treatment).

Search and select
A systematic review of the literature was performed to answer the following question: what are the (un)desirable effects of thromboprophylaxis with Direct Oral Anticoagulants (DOAC) or Low-Molecular-Weight Heparin (LMWH) in children with malignancy in whom systemic anticancer treatment was initiated, compared to placebo or standard of care?

P	**(Patients)**	pediatric patients with malignancy initiating systemic anticancer treatment
I	**(Intervention)**	thromboprophylaxis (DOAC or LMWH)
C	**(Comparison)**	placebo, standard of care (SOC)

O	**(Outcomes)**	venous thromboembolism (VTE, asymptomatic and symptomatic), major bleeding, mortality, catheter related thrombosis, post-thrombotic syndrome (PTS), quality of life, discontinuation of oncological treatment, postponing oncological treatment

Relevant outcome measures

The guideline development group considered mortality, VTE, major bleeding, quality of life and discontinuation of oncological treatment as critical outcome measures for decision making; and catheter related thrombosis, PTS and postponing oncological treatment as an important outcome measure for decision making.

The working group defined the outcome measures as follows:

- VTE: incidental/asymptomatic or symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE)
- Major bleeding: fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin levels of 1.24 mmol/L (20 g/L or greater) or more, or leading to a transfusion of red cells;

A priori, the working group did not define the other outcome measures listed above but used the definitions used in the studies.

The working group defined the following as a minimal clinically (patient) important difference:

- VTE, major bleeding and mortality: risk difference of 3%*
- For all other outcome measures, the default thresholds proposed by the international GRADE working group were used as a threshold for clinically relevant differences: a 25% difference in relative risk (RR) for dichotomous outcomes (RR <0.8 or RR >1.25), and 0.5 standard deviations (SD) for continuous outcomes.

**Based on the differences applied in the guidelines on thromboprophylaxis in patients with COVID-19. This working group derived the minimal clinically (patient) important differences from the ACCP (2012).*

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2013 until 7th March 2024. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 463 hits. Studies were selected based on the following criteria: (systematic reviews of) RCTs evaluating the effect of thromboprophylaxis with DOAC or LMWH in children with malignancy in whom systemic anticancer treatment was initiated compared to placebo or standard of care. 11 studies were initially selected based on title and abstract screening. After reading the full text, nine studies were excluded (see the table with reasons for exclusion under the tab Methods), and two studies were included (Rutjes, 2020 and O'Brien, 2024).

Results

Two studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

O'Brien (2024) performed a phase 3, open-label, randomized, controlled trial which was conducted in 74 pediatric hospitals in nine countries. In total, 512 patients aged one to 18 years with newly diagnosed acute lymphoblastic leukemia (pre-B cell or T cell) or lymphoblastic lymphoma (B cell or T cell immunophenotype) and a central venous line in place throughout induction, were included in the study. The 512 patients were randomly assigned to receive either SOC (n=256), or SOC plus prophylactic apixaban (n=256), daily for 29 days. The prophylactic apixaban dose regimen was age- and weight-based. The two groups were similar in their proportion of gender and acute lymphoblastic leukemia risk category (standard or high risk). The median follow-up was 27 days (IQR 26-28). The following relevant outcomes were reported: VTE, major bleeding, and mortality.

Rutjes (2020) included several RCT's in children, of which one fulfilled our inclusion criteria (Greiner, 2019). Greiner (2019) performed an open-label randomized controlled study which was conducted in 26 pediatric cancer centers in Germany and Switzerland. In total, 949 patients aged one to 18 years with newly diagnosed acute lymphoblastic leukemia were enrolled and randomized to receive low-dose unfractionated heparin (UFH, n=312), prophylactic low molecular weight heparin (enoxaparin) (n=317), or activity-adapted antithrombin (n=320) throughout induction therapy. The antithrombin group was not included in our literature analysis. Patients randomized in the UFH-group received standard of care, consisting of a low-dose UFH 2 IU/kg bodyweight/hour while the CVC was in use. Patients randomized in the enoxaparin group received enoxaparin at a dose of 80–100 IU/kg bodyweight once daily subcutaneously with a target anti-Xa level not exceeding 0.4 U/L, measured four hours after the third or fourth injection. The patients randomized in the UFH-group and the enoxaparin-group were comparable at baseline. The following outcomes were reported: symptomatic VTE, major bleeding, and survival.

Results

Venous thromboembolism

Total

O'Brien (2024) reported the outcome VTE, defined as the composite of non-fatal deep venous thrombosis (symptomatic or clinically unsuspected), pulmonary embolism, cerebral sinus venous thrombosis, and venous thromboembolism related death. VTE events were first confirmed by blinded adjudication solely based on imaging results and then further classified as symptomatic or clinically unsuspected based on the investigator's report. Symptomatic VTE events were included in the analysis if they occurred during the intended treatment period whereas asymptomatic VTE events were included in the analysis when screening research imaging studies were completed by day 40. No VTE-related death or pulmonary embolism occurred and there was only one case of cerebral sinus venous thrombosis in the SOC-group. In total, VTE-events occurred in 31 (12%) of the 256 patients receiving apixaban compared to 45 (18%) of the 256 patients receiving SOC. The risk ratio (RR, 95%CI) was 0.69 (0.45 to 1.05). The risk difference (RD, 95%CI) was -0.04 (-0.10 to 0.01, which was in favor of the apixaban group and considered to be clinically relevant.

Greiner (2019) reported on the outcome symptomatic VTEs, defined as symptomatic VTE and diagnosed based on clinical suspicion and confirmed by one or more suitable imaging methods within a routine diagnostic work-up.

Symptomatic VTE

O'Brien (2024) reported 4 (2%) non-fatal symptomatic VTE's in the apixaban group (N=256), compared to 6 (2%) VTEs in the SOC-group. The RR (95%CI) was 0.67 (0.19 to 2.33). Corresponding RD (95%CI) was -0.01 (-0.03 to 0.02), which was in favor of the apixaban group and not considered to be clinically relevant. Besides, one of the patients in the SOC-group had a fatal cerebral sinus venous thrombosis.

In the study of Greiner (2019) symptomatic VTE occurred in 11 (3.5%) of the 317 patients in the enoxaparin group and in 25 (8.0%) of the 312 patients that received SOC. The RR (95%CI) was 0.43 (0.22 to 0.86). Corresponding RD (95%CI) was -0.05 (-0.08 to -0.01), which was in favor of the enoxaparin group and considered to be clinically relevant.

Asymptomatic VTE

O'Brien (2024) reported 27 (11%) non-fatal clinically unsuspected VTE's in the apixaban group (N=256), compared to 38 (15%) VTEs in the SOC-group. The RR (95%CI) was 0.71 (0.45 to 1.13). Corresponding RD (95%CI) was -0.04 (-0.10 to 0.01), which was in favor of the apixaban group and considered to be clinically relevant.

Major bleeding

O'Brien (2014) reported on the outcome major bleeding, defined as fatal bleeding; clinically overt bleeding associated with a decrease in haemoglobin of at least 20 g/L (ie, 2 g/dL) in 24 hours; bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system; and bleeding that requires surgical intervention in an operating suite, including interventional radiology. Two major bleeding events occurred in each group (RR (95%CI) 1.0 (0.14 to 7.01) and RD (95%CI) 0.00 (-0.02 to 0.02)).

Greiner (2019) also reported on the outcome major bleeding, defined as hemorrhage meeting one or more of the following criteria: clinically evident, fatal, requiring erythrocyte replacement (10-20 ml/kg body weight), located within the cranium/spine, eye, retroperitoneum (diagnosis using magnetic resonance imaging, computed tomography and/or ultrasound) or severe or life-threatening event resulting from the hemorrhage, therefore requiring intensive care. Major bleeding occurred in one (0.5%) of the 317 patients that received enoxaparin and in four (1.1%) of the 312 patients that received SOC. The RR (95%CI) was 0.25 (0.03 to 2.19). Corresponding RD (95%CI) was -0.01 (-0.02 to 0.00), which was in favor of the enoxaparin group and was considered to be not clinically relevant.

Mortality

O'Brien (2014) reported on the outcome mortality, with one death occurring in the apixaban group and four deaths in the SOC-group. The RR (95%CI) was 0.25 (0.03 to 2.22). Corresponding RD (95%CI) was -0.01 (-0.03 to 0.01), which was in favor of the apixaban group and considered to be not clinically relevant. In the SOC-group, three participants died due to events that occurred during the treatment-emergent period ((infection [n=1], intracranial hemorrhage [n=1], and cardiac arrest [n=1]), and one due to an infection that occurred outside the treatment-emergent period. In the apixaban group there was one apixaban-related death (coagulopathy and hemorrhage after cardiac arrest of unknown cause).

Greiner (2019) reported on the outcome survival defined as time from diagnosis to the date of last follow-up or death from any cause – only exploratory analysis were available. The probability of overall survival at five years was similar in treatment arms (enoxaparin-group : 90.9±1.6%, SOC-group: 92.4±1.5%).

Catheter related thrombosis, post-thrombotic syndrome, quality of life, discontinuation of oncological treatment and postponing oncological treatment

None of the studies described these outcomes.

Level of evidence of the literature

Venous thromboembolism

Symptomatic

LMWH

Evidence regarding the outcome symptomatic VTE is derived from a RCT and therefore the level of evidence started as high. The level of evidence was downgraded to low. There was risk of bias (open label design; downgraded one level). Furthermore, the 95%CI of the effect estimate crossed one of the thresholds for clinical relevance (imprecision, downgraded one level).

DOAC

Evidence regarding the outcome symptomatic VTE is derived from a RCT and therefore the level of evidence started as high. The level of evidence was downgraded to very low. There was risk of bias (open label design; downgraded one level). Furthermore, confidence interval was very broad (serious imprecision, downgraded three levels).

Asymptomatic

LMWH

Since the included study did not report on the outcome asymptomatic VTE for thromboprophylaxis with LMWH, no GRADE conclusions could be drawn for this outcome.

DOAC

Evidence regarding the outcome asymptomatic VTE is derived from a RCT and therefore the level of evidence started as high. The level of evidence was downgraded to low. There was risk of bias (open label design; downgraded one level). Furthermore, the 95%CI of the effect estimate crossed one of the thresholds for clinical relevance (imprecision, downgraded one level).

Major bleeding

Evidence regarding the outcome major bleeding is derived from RCTs and therefore the level of evidence started as high. The level of evidence was downgraded to very low. There was risk of bias (open label design; downgraded one level) and the confidence interval was very broad (serious imprecision, downgraded three levels).

Mortality

LMWH

Since the included study did not report on the outcome mortality for thromboprophylaxis with LMWH, no GRADE conclusions could be drawn for this outcome.

DOAC

Evidence regarding the outcome mortality is derived from a RCT and therefore the level of evidence started as high. The level of evidence was downgraded to very low, because of a very broad confidence interval (serious imprecision, downgraded three levels).

Catheter related thrombosis, post-thrombotic syndrome, quality of life, discontinuation of oncological treatment and postponing oncological treatment

Since none of the included studies reported on the outcomes catheter related thrombosis, post-thrombotic syndrome, quality of life, discontinuation of oncological treatment and postponing oncological treatment related thrombosis, no GRADE conclusions could be drawn for those outcomes.

Conclusions

General remarks

These studies included children with hematological malignancies. Therefore, the results might not be applicable to all children with malignancy who are initiating systemic anticancer treatment.

Venous thromboembolism

LMWH

Low GRADE	*Symptomatic VTE* Thromboprophylaxis with LMHW may result in a reduction of symptomatic VTE when compared with standard of care in pediatric patients with hematological malignancy initiating systemic anticancer treatment. *Asymptomatic VTE* No evidence was found regarding the effect of thromboprophylaxis with LMWH on the incidence of asymptomatic VTE when compared with standard of care in pediatric patients with hematological malignancy initiating systemic anticancer treatment *Source: Greiner, 2019*
No GRADE	

DOAC

Very low GRADE	*Symptomatic VTE* The evidence is very uncertain about the effect of thromboprophylaxis with DOAC on the outcome symptomatic VTE when compared with standard of care in pediatric patients with hematological malignancy initiating systemic anticancer treatment. *Asymptomatic VTE* Thromboprophylaxis with DOAC may result in a reduction of asymptomatic VTE when compared with standard of care in pediatric patients with hematological malignancy initiating systemic anticancer treatment. *Source: O'Brien, 2024*
Low GRADE	

Major bleeding

Very low GRADE	The evidence is very uncertain about the effect of thromboprophylaxis with DOAC or LMWH on the outcome major bleeding when compared with standard of care in pediatric patients with hematological malignancy initiating systemic anticancer treatment. *Source: O'Brien, 2024; Greiner, 2019*

Mortality

DOAC

Very low GRADE	The evidence is very uncertain about the effect of thromboprophylaxis with DOAC on the outcome mortality when compared with standard of care in pediatric patients with hematological malignancy initiating systemic anticancer treatment. *Source: O'Brien, 2024*

LMWH

No GRADE	No evidence was found regarding the effect of thromboprophylaxis with LMWH when compared with standard of care in pediatric patients with hematological malignancy initiating systemic anticancer treatment. *Source: none*

Catheter related thrombosis, post-thrombotic syndrome, quality of life, discontinuation of oncological treatment and postponing oncological treatment

No GRADE	No evidence was found regarding the effect of thromboprophylaxis on the incidence of catheter related thrombosis, post-thrombotic syndrome, quality of life, discontinuation of oncological treatment and postponing oncological treatment when compared with standard of care in pediatric patients with malignancy initiating systemic anticancer treatment. *Source: None*

Overwegingen – van bewijs naar aanbeveling

<u>Voor- en nadelen van de interventie en de kwaliteit van het bewijs</u>

In totaal zijn er twee RCT's gevonden die hebben gekeken naar de effecten van tromboseprofylaxe met Directe orale Anticoagulantia (DOAC) of Laag Moleculair Gewicht Heparine (LMWH) in kinderen met een hematologische maligniteit bij wie een systemische oncologische behandeling werd gestart, in vergelijking met placebo of standaardzorg. Hiervan heeft één fase 3-studie het effect van profylactisch apixaban onderzocht en de andere studie het effect van profylactisch enoxaparine.

De bewijskracht van de resultaten werd gelimiteerd door risico op bias, vanwege het gegeven dat patiënt, lokale onderzoekers en behandelaren niet geblindeerd waren voor de toegekende interventie. Daarnaast werd de bewijskracht gelimiteerd door (ernstige) imprecisie. Tromboseprofylaxe met enoxaparine zou kunnen leiden tot minder symptomatische veneuze trombo-embolieën (VTE, cruciale uitkomst), vergeleken met standaardzorg. De bewijskracht is laag. Voor de cruciale uitkomstmaat ernstige bloedingen is de bewijskracht zeer laag en voor de cruciale uitkomstmaten sterfte zijn er slechts gegevens uit exploratieve analyses beschikbaar en voor asymptomatische VTE's zijn er geen gegevens beschikbaar.

Tromboseprofylaxe met apixaban zou kunnen leiden tot een reductie in asymptomatische VTE's, vergeleken met standaardzorg (cruciale uitkomstmaat). De bewijskracht is laag. Voor de cruciale uitkomstmaten majeure bloeding, symptomatische VTE's en sterfte zijn we onzeker over het effect van tromboseprofylaxe met apixaban (bewijskracht zeer laag). Er zijn geen studies gevonden die de cruciale uitkomstmaten kwaliteit van leven en staken van de oncologische behandeling, en belangrijke uitkomstmaten katheter gerelateerde trombose, post trombotisch syndroom (PTS), en uitstellen van de oncologische behandeling beschreven. Er is voor deze cruciale en belangrijke uitkomstmaten daarom geen bewijs gevonden. De algehele bewijskracht is zeer laag. Er is dus sprake van een kennisvraag.

Beide studies (Greiner, 2019 en O'Brien, 2024) includeerden patiënten met een hematologische maligniteit, voornamelijk kinderen met acute lymfatische leukemie. Het is onzeker of de gevonden resultaten ook toepasbaar zijn op kinderen met andere maligniteiten, zoals kinderen met een solide maligniteit.

Dat kinderen met een maligniteit een verhoogd risico hebben op trombose is bekend (Barg, 2020). De *Scientific and Standardization Committee* van de *International Society on Thrombosis and Haemostasis* (ISTH) heeft getracht een risicoprofiel te schetsen (Tullius, 2018) waarbij patiëntkarakteristieken, ziekte gerelateerde factoren en behandeling gerelateerde factoren worden meegewogen.
Gezien de lage bewijskracht van de resultaten uit de geïncludeerde studies is het advies van de werkgroep om de aanbevelingen van de ISTH te volgen (Tullius, 2018). Deze zijn als volgt geformuleerd:

1. We raden aan om bij elke kind met een maligniteit bij diagnose een risico inschatting voor trombose te maken;
2. Bij kinderen die geen trombose in de voorgeschiedenis hebben, raden we af om routinematig te starten met trombose profylaxe;
3. Wij bevelen tromboseprofylaxe aan bij kinderen met een maligniteit én een doorgemaakte trombose die intensieve therapie ondergaan, zolang er geen contra-indicaties zijn voor antistolling;
4. We suggereren dat trombose profylaxe bij kinderen zonder een doorgemaakte trombose overwogen moet worden op individuele basis, op basis van een combinatie van risicofactoren versus de contra-indicaties voor antistolling. Risicofactoren voor trombose bij kinderen met een maligniteit zijn: centraal veneuze lijn (CVL), asparaginase, obesitas, adolescentie, hormonale anticonceptie of ziekenhuisopname voor chirurgie.

Bij kinderen met een maligniteit worden bijna alle centraal veneuze katheters (CVL) in de bovenste lichaamshelft geplaatst. De lokalisatie van de katheter blijkt een belangrijke risicofactor voor trombose. Het is bekend dat een CVL het risico op trombose verhoogt. Katheters geplaatst in de vena subclavia, Peripherally Inserted Central Catheter (PICC-) lijnen en linkszijdig geplaatste katheters leiden tot een groter risico op katheter-gerelateerde trombose dan katheters die aan de rechterzijde en in de vena jugularis zijn ingebracht (Albisetti, 2013; Pelland-Mercotte 2019).
Behandeling met asparaginase is een risicofactor voor trombose (Athale 2014). In geval van trombose wordt de behandeling met asparaginase vaak tijdelijk onderbroken. Aanbevolen wordt om nadien te herstarten, indien er gelijktijdig secundaire trombose profylaxe gegeven wordt (Hijiya 2016). Hoewel de literatuur niet eenduidig is over de rol van erfelijke trombofilie, is het wel duidelijk dat bij kinderen de pathogenese van maligniteit geassocieerde trombose multifactorieel is (Ruiz-Llobet, 2013; Barg, 2022).
In de literatuur worden verschillende leeftijdsgrenzen aangehouden zoals > 10 jaar, > 14 jaar of adolescentie. In navolging van andere modules uit de richtlijn Antitrombotisch beleid handhaven we de leeftijdsgrens van 12 jaar. Omdat typen maligniteit en chemokuren verschillen tussen kinderen en volwassenen, wordt in deze specifieke patiëntengroep niet geadviseerd om de richtlijnen voor volwassenen te volgen bij kinderen >12 jaar.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>
Er is weinig onderzoek gedaan naar de waarden en voorkeuren van patiënten en hun verzorgers. In Nederland is LMWH tot nog toe het middel van eerste keus voor primaire tromboseprofylaxe en tolerantie speelt in de huidige, dagelijkse praktijk zeker een rol. Uit de studie van Greiner (2019) blijkt dat de therapie met subcutane injecties (namelijk LMWH) door kinderen en ouders als onprettig wordt ervaren. De optie LMWH leidde ertoe dat ouders op voorhand niet wilden deelnemen. En een derde van de ouders weigerde na loting alsnog de LMWH voor hun kind.
Uit literatuur over tromboseprofylaxe bij volwassenen blijkt dat 62% van de patiënten met een maligniteit geen informatie had gekregen over het verhoogde risico op VTE (Potere,

2022). Voor kinderen ontbreken hierover gegevens in de literatuur. Het is aannemelijk dat, in analogie met volwassenen, ook kinderen en hun ouders een verkleining van het risico op trombose wensen. Ook bij kinderen wordt het tromboserisico tegen het bloedingsrisico afgewogen, waarbij opgemerkt moet worden dat kinderen een lager bloedingsrisico hebben. Daarnaast moet tromboseprofylaxe in verhouding staan tot de dagelijkse belasting van de toediening van LMWH. Een DOAC zou de keuze makkelijker kunnen maken gezien dit oraal, als tablet of drank, gegeven kan worden. Hierbij dient wel in ogenschouw genomen te worden dat een DOAC niet voor iedere patiënt een optie is, bijvoorbeeld vanwege interactie met (profylactische of therapeutische) azolen die sommige patiënten tijdens hun oncologische behandeling krijgen.
Van alle kinderen met trombose ontwikkelt circa 25% een posttrombotisch syndroom (PTS) welke de levenskwaliteit vermindert en van invloed kan zijn op het dagelijks functioneren in de maatschappij. Een centrale lijn, volledige occlusie van het vat en onvolledige rekanalisatie na behandeling zijn prognostische factoren voor PTS (Engel, 2020). Een studie naar de ontwikkeling van posttrombotisch syndroom ten gevolge van een Port-a-cath gerelateerde trombose in 45 van de 114 kinderen toonde milde PTS in 5,6% van de patiënten na een gemiddelde follow up van 4,2 jaar (Albisetti, 2013).

Kosten (middelenbeslag)
Er is geen literatuur met betrekking tot een kosteneffectiviteitsanalyse naar tromboseprofylaxe bij kinderen met een maligniteit. Voor jonge kinderen betreft het altijd bereidingen van de LMWH, wat voorbehouden is aan enkele apotheken. Diverse DOACs zijn geregistreerd voor kinderen, maar zijn niet altijd in een suspensie beschikbaar.

Aanvaardbaarheid, haalbaarheid en implementatie
Sinds 2018 is de kinderoncologische zorg in Nederland geconcentreerd in het Prinses Maxima Centrum. Op basis van beschikbare literatuur zou de eerste stap zijn dat bij ieder kind met een nieuw gediagnosticeerde maligniteit een inschatting gemaakt wordt van het trombose risico. Daarnaast kan meer aandacht besteed worden aan comfortzorg bij de toediening van de subcutane injecties, te weten helpend taalgebruik, de shot-blocker, buzzy en andere hulpmiddelen. Bovengenoemde maatregelen zouden ook in studieverband kunnen worden geïmplementeerd.

Aanbeveling

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Er is te weinig bewijs om bij alle kinderen met een maligniteit te starten met tromboseprofylaxe om trombose te voorkomen. Belangrijkste argument is dat het risico op trombose bij kinderen in het algemeen veel lager is dan bij volwassenen. Omdat trombose kan leiden tot mortaliteit en morbiditeit, heeft deze complicatie de laatste jaren meer aandacht gekregen. Nadelen van tromboseprofylaxe zijn het bloedingsrisico en de belasting van dagelijks subcutane injecties. De opkomst van het gebruik van DOAC bij kinderen maken dit laatste argument minder relevant. Aanbevolen wordt om per patiënt een inschatting te maken van tromboserisico door naar bijkomende risicofactoren voor trombose te vragen.

Informeer het kind en de ouders (naasten/verzorgers) over het risico op trombose, eventueel gebruik van antistollingsmiddelen en breng de risicofactoren voor trombose in kaart.

Overweeg tromboseprofylaxe bij:
- kinderen met een trombose in de voorgeschiedenis;

- kinderen ouder dan 12 jaar die een centraal veneuze lijn hebben en twee of meer bijkomende risicofactoren voor VTE. Bekende risicofactoren zijn een positieve familieanamnese, behandeling met asparaginase, obesitas, hormonale anticonceptie of recente chirurgie.

Kennisvragen

Wat zijn de (on)gewenste effecten van tromboseprofylaxe met DOACs of LMWH bij kinderen met een maligniteit bij wie systemische behandeling is gestart, vergeleken met placebo of standaardzorg?

Literatuur

Athale U. Thrombosis in pediatric cancer: identifying the risk factors to improve care. Expert Rev Hematol. 2013 Oct;6(5):599-609. doi: 10.1586/17474086.2013.842124. PMID: 24125523.

Albisetti M, Kellenberger CJ, Bergsträsser E, Niggli F, Kroiss S, Rizzi M, Schmugge M. Port-a-cath-related thrombosis and postthrombotic syndrome in pediatric oncology patients. J Pediatr. 2013 Nov;163(5):1340-6.

Barg AA, Kenet G. Cancer-associated thrombosis in pediatric patients. Thromb Res. 2020 Jul;191 Suppl 1:S22-S25. doi: 10.1016/S0049-3848(20)30392-3. PMID: 32736773D.

O'Brien SH, Rodriguez V, Lew G, Newburger JW, Schultz CL, Orgel E, Derr K, Ranalli MA, Esbenshade AJ, Hochberg J, Kang HJ, Dinikina Y, Mills D, Donovan M, Dyme JL, Favatella NA, Mitchell LG; PREVAPIX-ALL investigators. Apixaban versus no anticoagulation for the prevention of venous thromboembolism in children with newly diagnosed acute lymphoblastic leukaemia or lymphoma (PREVAPIX-ALL): a phase 3, open-label, randomised, controlled trial. Lancet Haematol. 2024 Jan;11(1):e27-e37. doi: 10.1016/S2352-3026(23)00314-9. Epub 2023 Nov 16. Erratum in: Lancet Haematol. 2024 Jun;11(6):e399. doi: 10.1016/S2352-3026(24)00113-3. PMID: 37980924.

Engel ER, Nguyen ATH, Amankwah EK, Albisetti M, Brandão LR, Goldenberg NA, Betensky M. Predictors of postthrombotic syndrome in pediatric thrombosis: A systematic review and meta-analysis of the literature. J Thromb Haemost. 2020 Oct;18(10):2601-2612.

Hijiya N, van der Sluis IM. Asparaginase-associated toxicity in children with acute lymphoblastic leukemia. Leuk Lymphoma. 2016;57(4):748-57. doi: 10.3109/10428194.2015.1101098. Epub 2015 Nov 20. PMID: 26457414; PMCID: PMC4819847.

Greiner J, Schrappe M, Claviez A, Zimmermann M, Niemeyer C, Kolb R, Eberl W, Berthold F, Bergsträsser E, Gnekow A, Lassay E, Vorwerk P, Lauten M, Sauerbrey A, Rischewski J, Beilken A, Henze G, Korte W, Möricke A; THROMBOTECT Study Investigators. THROMBOTECT - a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents. Haematologica. 2019 Apr;104(4):756-765. doi: 10.3324/haematol.2018.194175. Epub 2018 Sep 27. PMID: 30262570; PMCID: PMC6442986.

Neville JJ, Aye HM, Hall NJ. Tunnelled external versus implanted port central venous catheters in paediatric oncology: a systematic review and meta-analysis. Arch Dis Child. 2023 Dec;108(12):975-981

Pelland-Marcotte MC, Tole S, Pechlivanoglou P, Brandã o LR. Effectiveness and Safety of Primary Thromboprophylaxis in Children with Cancer: A Systematic Review of the Literature and Network Meta-Analysis. Thromb Haemost. 2019 Dec;119(12):2034-2042. doi: 10.1055/s-0039-1697027. Epub 2019 Oct 10. PMID: 31600808.

Potere N, Barco S, Mahé I, Cesarman-Maus G, Angchaisuksiri P, Leader A, Okoye HC, Olayemi E, Ay C, Carrier M, Connors JM, Farmakis IT, Fumagalli RM, Jing ZC, Lee LH, McLintock C, Ní Ainle F, Giannakoulas G, Goto S, Guillermo Esposito MC, Jara-Palomares L, Szlaszynska M, Tan CW, Van Es N, Wang TF, Hunt BJ, Di Nisio M. Awareness of venous thromboembolism among patients with cancer: Preliminary findings from a global initiative for World Thrombosis Day. J Thromb Haemost. 2022 Dec;20(12):2964-2971. doi: 10.1111/jth.15902. Epub 2022 Oct 21. PMID: 36201366; PMCID: PMC9828201.

Ruiz-Llobet A, Gassiot S, Sarrate E, Zubicaray J, Dapena JL, Rives S, Sevilla J, Menárguez López Á, Panesso Romero M, Montoya C, Vagace JM, Molina Hurtado JR, García-Morín M, García Abós M, Mendoza Sánchez MC, Lendínez F, Palomo Moraleda P, Tallón M, González B, Urrutia E, Serna JV, Peláez Pleguezuelos I, Martínez Merino M, Ramos Elbal E, Orellana E, Benítez Muñoz H, Berrueco R. Venous thromboembolism in pediatric patients with acute lymphoblastic leukemia under chemotherapy treatment. Risk factors and usefulness of thromboprophylaxis. Results of LAL-SEHOP-PETHEMA-2013. J Thromb Haemost. 2022 Jun;20(6):1390-1399.

Rutjes AW, Porreca E, Candeloro M, Valeriani E, Di Nisio M. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database Syst Rev. 2020 Dec 18;12(12):CD008500. doi: 10.1002/14651858.CD008500.pub5. PMID: 33337539; PMCID: PMC8829903.

Tullius BP, Athale U, van Ommen CH, Chan AKC, Palumbo JS, Balagtas JMS; Subcommittee on Hemostasis and Malignancy and the Subcommittee on Pediatric/Neonatal Thrombosis and Hemostasis. The identification of at-risk patients and prevention of venous thromboembolism in pediatric cancer: guidance from the SSC of the ISTH. J Thromb Haemost. 2018 Jan;16(1):175-180

Bijlagen bij module tromboseprofylaxe kinderen met een maligniteit

Implementatieplan

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijke kennisvraag
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	**Sterkte van de aanbeveling**	**Bewijskracht per uitkomstmaat**	**Verkeerslicht per (sub)aanbeveling**
Informeer het kind en de ouders (naasten/verzorgers) over het risico op trombose, eventueel gebruik van antistollingsmiddelen en breng de risicofactoren	□ Sterk (doe/ gebruik) / **X** Zwak (overweeg)	**Overall bewijskracht** □ **H** □ **M** □ **L X VL** □ **NG** **Range bewijskracht van alle uitkomstmaten** □ **H** □ **M X L X VL** **X NG**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in **X ORANJE:** gebruik tabel B

voor trombose in kaart. Overweeg tromboseprofylaxe bij: • kinderen met een trombose in de voorgeschiedenis ; • kinderen ouder dan 12 jaar die een centraal veneuze lijn hebben en twee of meer bijkomende risicofactoren voor VTE. Bekende risicofactoren zijn een positieve familieanamnese, behandeling met asparaginase, obesitas, hormonale anticonceptie of recente chirurgie.		**OF** □ **voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	□ **LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in

Implementatietabel

Aanbeveling Informeer het kind en de ouders (naasten/verzorgers) over het risico op trombose, eventueel gebruik van antistollingsmiddelen en breng de risicofactoren voor trombose in kaart. Overweeg tromboseprofylaxe bij: • kinderen met een trombose in de voorgeschiedenis; kinderen ouder dan 12 jaar die een centraal veneuze lijn hebben en twee of meer bijkomende risicofactoren voor VTE. Bekende risicofactoren zijn een positieve familieanamnese, behandeling met asparaginase, obesitas, hormonale anticonceptie of recente chirurgie	Op basis van de beschikbare evidentie en ervaring uit de praktijk kon er onvoldoende richting aan de besluitvorming worden gegeven. Om die reden is er geen beschrijving van belemmeringen en kansen voor implementatie van de aanbeveling toegevoegd. Disseminatie van de kennis in deze module verloopt via de standaard route. De module wordt gepubliceerd op de Richtlijnendatabase.

Evidence tables

Evidence table for intervention studies (randomized controlled trials and non-randomized *observational* studies [cohort studies, case-control studies, case series])

Research question: What are the (un)desirable effects of thromboprophylaxis with Direct Oral Anticoagulants (DOAC) or Low-Molecular-Weight Heparin (LMWH) in children with malignancy in whom systemic anticancer treatment was initiated, compared to placebo or standard of care?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
O'Brien, 2024	Type of study: Phase 3, open-label, randomised, controlled trial Setting and country: 74 paediatric hospitals in 9 countries (USA, Australia, Canada, Belgium, Czech Republic, Hungary, Mexico, Poland, Russia, and South Korea). Recruitment	Inclusion criteria: - Aged ≥ 1 year to < 18 years. - With newly diagnosed acute lymphoblastic leukaemia (pre-B cell or T cell) or lymphoblastic lymphoma (B cell or T cell immunophenotype) and a central venous line in place throughout induction. - Patients receiving planned induction chemotherapy with a corticosteroid, vincristine, and single or multiple doses of asparaginase, with or without an anthracycline, were	Describe intervention (treatment/procedure/test): Prophylactic apixaban in addition to standard acute lymphoblastic leukaemia or lymphoma treatment. Details: Weight- and age-adjusted twice-daily apixaban during induction. Participants ≤ 35 kg were administered 2·5 mg twice daily of apixaban as a 2·5 mg tablet, 0·5 mg tablets, or 0·4 mg/mL oral solution, while those > 35 kg were administered weight-adjusted prophylactic doses using 0·5 mg tablets or the 0·4 mg/mL oral solution twice daily. Children < 5 years could	Describe control (treatment/procedure/test): Standard of care (SOC, i.e., no systematic anticoagulation)	Length of follow-up: Median follow-up of 27 days (IQR 26-28). Loss-to-follow-up: Intervention: 14/256 (5.5%) Reasons (describe) - Withdrew consent (13) - Died (1) Control: 7/256 (2.7%) Reasons (describe) - Withdrew consent (3) - Died (2) - Lost to follow-up (1) - Other (1) Incomplete outcome data: Intervention: 58/256 (22.7%) Reasons (describe)	Outcome measures and effect size (include 95%CI and p-value if available): Venous thromboembolism, (n/N (%)): Defined as the composite of non-fatal deep venous thrombosis (symptomatic or clinically unsuspected), pulmonary embolism, cerebral sinus venous thrombosis, and venous thromboembolism related death. I: 31/256 (12%) C: 45/256 (18%) *Relative risk (95% CI): 0.69 (0.45 - 1.05)* Major bleeding (n/N (%)) Defined as defined as fatal bleeding; clinically overt bleeding associated with a decrease in haemoglobin of	from article: *No statistically significant treatment benefit was identified in participants receiving apixaban.*

	was from Oct 22, 2015, to June 4, 2021. Funding: Funded by Bristol Myers Squibb-Pfizer Alliance. The funders contributed to the study design, data collection, data analysis, data interpretation, writing of the manuscript and had an opportunity to review and comment on the manuscript before submission and during peer review. There are several COIs in this study, e.g. multiple authors are employees of the funder	eligible. <u>Exclusion criteria</u>: - Participants with an increased risk of bleeding. - Extreme hyperleukocytosis - Major surgery within 7 days of enrolment - Scheduled to undergo more than three lumbar punctures during the treatment period (ie, day 1 to day 29). - international normalized ratio greater than 1·4 and activated partial thromboplastin time greater than 3 above the upper limit of normal for age within one week before enrolment. - History of venous thromboembolism, organ dysfunction (i.e., liver or renal), or severe uncontrolled hypertension at the time of enrolment. - Concurrent thromboprophylaxis or antiplatelet therapy.	not receive apixaban oral solution.		Discontinued study treatment - Adverse events (35) - Withdrew consent (12) - Requested to discontinue treatment (8) - No longer met study criteria (2) - Other (1) Control: 11/256 N (%) 4.3% Reasons (describe) Discontinued study before day 29 visit: - Adverse events (5) - Withdrew consent (3) - Requested to discontinue treatment (2) - Other (1) <u>Overall:</u> Intervention: Analysed: 256 Complete imaging data: 219 Control: Analysed: 256 Complete imaging data: 219	at least 20 g/L (ie, 2 g/dL) in 24 h; bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system; and bleeding that requires surgical intervention in an operating suite, including interventional radiology I: 2/256 (1%) C: 2/256 (1%) *Relative risk (95% CI):* *1.0 (0.14 – 7.01)* <u>Mortality (n/N (%)):</u> No definition provided. Five deaths occurred during the study. There was one apixaban-related death (coagulopathy and haemorrhage after cardiac arrest of unknown cause, as described previously). In the SOC group, three participants died due to events that occurred during the treatment-emergent period (infection [n=1], intracranial haemorrhage [n=1], and cardiac arrest [n=1]), and one due to an infection that occurred outside the treatment-emergent period. I: 1/256 (0.4%) C: 4/256 (1.6%)	

	(and provider of the treatment).	<u>N total at baseline</u>: Intervention: 256 Control: 256 <u>Important prognostic factors[2]</u>: <u>age (median (IQR)</u> I: 6 (4-11) C: 6 (3-11) <u>Age categorisation, years:</u> 1 to <2 years I: <1% C: 3% 2 to < 6 years I: 46% C: 43% 6 to <12 years I: 34% C: 32% 12 to ≤18: years I: 19% C: 22% <u>Sex:</u> I: 55% M C: 58% M <u>Subtype of lymphoblastic leukaemia or lymphoma</u> B-cell I: 88% C: 88% T-cell I: 11% C: 11%					

		Other I: 1% C: 1% Groups comparable at baseline? Yes					

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Rutjes, 2020 Study characteristics and results are extracted from the SR, for details see study characteristics in Rutjes (2020).	SR and meta-analysis of RCTs *Literature search up to August 2020* <u>Included studies</u> Greiner, 2019 <u>Study design</u>: Open-label RCT <u>Setting and Country</u>: Multicentre study, 26 centres in Germany and Switzerland <u>Source of funding and conflicts of interest:</u> Interventional drugs were provided free of charge by	Inclusion criteria SR: RCT's and quasi-RCT's on participants who were ambulatory patients receiving chemotherapy at the time of randomisation or study entry. Intervention: Any type of oral or parenteral coagulation. Exclusion criteria SR: Studies of participants receiving anticoagulation for a previous VTE or an indication other than VTE. Studies evaluating prophylaxis for catheter-related thrombosis. *Total of 32 studies included in qualitive analysis, 19 studies*	Prophylactic LMWH, enoxaparin at a dose of 80–100 IU/kg bodyweight once daily SC with a target anti-Xa level not exceeding 0.4 U/L, measured 4 hours after the third or fourth injection. Thromboprophylaxis was started on day eight and ended on day 33 of induction chemotherapy.	Standard of care: low-dose UFH 2 IU/kg bodyweight/hour	<u>End-point of follow-up (median)</u>: NR <u>For how many participants were no complete outcome data available?</u>	*For all analyses: pooled effect is NA (since only one of the studies in Rutjes (2020) will be included in our analysis*. <u>Symptomatic VTE</u> Defined as objectively verified by means of Doppler (compression) ultrasonography or venography for DVT, and spiral computed tomography, ventilation/perfusion lung scan, or pulmonary angiography for PE. *LMWH (RR (95%CI))* I: I : 11 (3.5) C: 25 (8.0) RR: 0.41 (0.20 to 0.85) <u>Any VTE</u> Defined as symptomatic and incidental VTE	<u>Author's conclusion</u> In ambulatory cancer patients, primary thromboprophylaxis with direct factor Xa inhibitors may reduce the incidence of symptomatic venous thromboembolism (VTE) (low-certainty evidence) and probably increases the risk major bleeding (moderate-certainty evidence) when compared with placebo. Low-molecular-weight heparin (LMWH) reduces symptomatic VTE with 37 participants requiring prophylaxis to prevent one event (high-certainty evidence). This benefit comes at the cost of a higher incidence of major bleeding, where for each 144 participants treated, one event is expected to occur when compared against

	pharmaceutical companies, but neither of them was involved in the study nor in writing the manuscript. No relevant COI.	*included in meta-analysis. Since part of these studies did not fulfil our inclusion criteria, we described one study (Greiner, 2019) in this evidence table.* <u>Important patient characteristics at baseline</u>: <u>N</u> N=949 ,of which N=312 received UFH and N=317 received enoxaparin. Other N=320 were randomized to antithrombin. Those patients were not included in our literature analysis. <u>Age (mean years±SD)</u> NR *(54% aged 1–6 years, 19.8% 6–10 years, 26.2% > 10 years)* <u>*Sex (% male)*</u>*:* 56.6 <u>*Metastatic disease (%):*</u> N.A. (haematological cancer) <u>*Previous VTE (n (%)):*</u> NR <u>*Disease characteristics*</u>				*LMWH (RR (95%CI))* NR <u>Major bleeding</u> Defined as overt bleeding associated with a decrease in haemoglobin of 2 g/dL or more, or leading to a transfusion of two or more units of packed red blood cells or whole blood; bleeding that occurred at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or bleeding contributing to death. *LMWH (RR (95%CI))* I : 1 (0.5) C : 4 (1.1) RR : NR <u>Clinically relevant bleeding</u> Defined as major and clinically relevant nonmajor bleeding); typically defined as overt bleeding that does not meet the criteria for major bleeding, but is associated with the need for medical intervention, contact with a physician, or interruption of the study drug or with discomfort or impairment of activities of daily life	placebo or no thromboprophylaxis (moderate-certainty evidence). When deciding whether to use primary antithrombotic prophylaxis in ambulatory cancer patients receiving chemotherapy, clinicians need to determine the patient's baseline risk of VTE with the help of risk-stratification models and weigh the magnitude of benefit with antithrombotic prophylaxis, especially on major clinical endpoints, against the risk of major bleeding complications. Evidence for the use of thromboprophylaxis with anticoagulants other than direct factor Xa inhibitors and LMWH is limited. <u>Remarks on individual studies</u> RoB assessment on Greiner (2019): open label study, therefore high risk on performance bias and detection bias.

		Groups comparable at baseline? Yes				*LMWH (RR (95%CI))* NR <u>Mortality</u> Survival was defined as time from diagnosis to the date of last follow-up or death from any cause – only exploratory analysis were available. *LMWH* The probability of overall survival at 5 years was similar in treatment arms (I : 90.9±1.6%, C: 92.4±1.5%). <u>Quality of life</u> NR <u>Arterial thromboembolic events.</u> NR <u>Thromboembolism</u> Defined as symptomatic thromboembolism, based on clinical suspicion and had to be confirmed by one or more suitable imaging methods within a routine diagnostic work-up. Intermittent dysfunction of the CVC by a clot at the tip of the catheter was not considered a thrombotic event as long as CVC patency was restored *LMWH (RR (95%CI))* I : 11 (3.5) C: 25 (8.0) RR: 0.41 (0.20 to 0.85)	

Table of excluded studies

Reference	Reason for exclusion
Kahale LA, Tsolakian IG, Hakoum MB, Matar CF, Barba M, Yosuico VE, Terrenato I, Sperati F, Schünemann H, Akl EA. Anticoagulation for people with cancer and central venous catheters. Cochrane Database Syst Rev. 2018 Jun 1;6(6):CD006468. doi: 10.1002/14651858.CD006468.pub6. PMID: 29856471; PMCID: PMC6389340.	Other more complete reviews available. Included two trials in children (Ruud, 2006 (wrong intervention: VKA) and Massicotte, 2003 (wrong population: 51% had cancer).
Pelland-Marcotte MC, Tole S, Pechlivanoglou P, Brandão LR. Effectiveness and Safety of Primary Thromboprophylaxis in Children with Cancer: A Systematic Review of the Literature and Network Meta-Analysis. Thromb Haemost. 2019 Dec;119(12):2034-2042. doi: 10.1055/s-0039-1697027. Epub 2019 Oct 10. PMID: 31600808.	Cochrane Review of Rutjes (2020) is more recently performed.
Pedersen LH, Villadsen GB, Hellfritzsch M, Hvas AM. Prophylaxis of Venous Thromboembolism in Children: A Systematic Review. Semin Thromb Hemost. 2022 Jun;48(4):413-421. doi: 10.1055/s-0042-1748151. Epub 2022 Jun 30. PMID: 35772401.	Seems to be an incomplete review. Included only three studies (Elhasid, 2001; Meister, 2008 and Masicotte, 2003 (wrong population: 51% had cancer).
Greiner J, Schrappe M, Claviez A, Zimmermann M, Niemeyer C, Kolb R, Eberl W, Berthold F, Bergsträsser E, Gnekow A, Lassay E, Vorwerk P, Lauten M, Sauerbrey A, Rischewski J, Beilken A, Henze G, Korte W, Möricke A; THROMBOTECT Study Investigators. THROMBOTECT - a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents. Haematologica. 2019 Apr;104(4):756-765. doi: 10.3324/haematol.2018.194175. Epub 2018 Sep 27. PMID: 30262570; PMCID: PMC6442986.	Included in Pelland-Marcotte, 2019 en Rutjes, 2020
Abate ME, Sánchez OE, Boschi R, Raspanti C, Loro L, Affinito D, Cesari M, Paioli A, Palmerini E, Ferrari S. Analysis of risk factors for central venous catheter-related complications: a prospective observational study in pediatric patients with bone sarcomas. Cancer Nurs. 2014 Jul-Aug;37(4):292-8. doi: 10.1097/NCC.0b013e31829627e7. PMID: 23782516.	Wrong study design (cohort study)
Pelland-Marcotte MC, Amiri N, Avila ML, Brandão LR. Low molecular weight heparin for prevention of central venous catheter-related thrombosis in children. Cochrane Database Syst Rev. 2020 Jun 18;6(6):CD005982. doi: 10.1002/14651858.CD005982.pub3. PMID: 32557627; PMCID: PMC7390480.	Included two trials in children (Masicotte, 2003 (wrong study population: 51% had cancer) and Greiner, 2019
Hansen RS, Nybo M, Hvas AM. Venous Thromboembolism in Pediatric Cancer Patients with Central Venous Catheter-A Systematic Review and Meta-analysis. Semin Thromb Hemost. 2021 Nov;47(8):920-930. doi: 10.1055/s-0041-1729886. Epub 2021 Sep 2. PMID: 34474495.	Did not perform analysis on comparison between thromboprofylaxis vs no thromboprofylaxis.
Hsiao W, Krava E, Wee CP, Chau E, Jaffray J. The incidence and risk factors for venous thromboembolism in adolescent and young adult oncology patients. Pediatr Blood Cancer. 2021 May;68(5):e28957. doi: 10.1002/pbc.28957. Epub 2021 Feb 24. PMID: 33624938.	Wrong outcomes (incidence, risk factors and outcomes of VTE in oncology patients)
Tuckuviene R, Ranta S, Albertsen BK, Andersson NG, Bendtsen MD, Frisk T, Gunnes MW, Helgestad J, Heyman	Did not report on characteristics for LMWH vs no LMWH. Did only report:

MM, Jonsson OG, Mäkipernaa A, Pruunsild K, Tedgård U, Trakymiene SS, Ruud E. Prospective study of thromboembolism in 1038 children with acute lymphoblastic leukemia: a Nordic Society of Pediatric Hematology and Oncology (NOPHO) study. J Thromb Haemost. 2016 Mar;14(3):485-94. doi: 10.1111/jth.13236. Epub 2016 Jan 30. PMID: 26707629.	no major bleedings in LMWH/VKA-treated patient. Patients could also have received UFH or systemic thrombolysis.

Literature search strategy

Zoekverantwoording

5 ***Algemene informatie***

Cluster/richtlijn: Antitrombotisch beleid – UV4 Tromboseprofylaxe bij kinderen met een maligniteit	
Uitgangsvraag/modules: Wat is de optimale tromboseprofylaxe bij (opgenomen) kinderen met een maligniteit?	
Database(s): Embase.com, Ovid/Medline	Datum: 7-3-2024
Periode: vanaf 2013	Talen: geen restrictie
Literatuurspecialist: Esther van der Bijl	Rayyan review: https://rayyan.ai/reviews/955843
BMI-zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht op de elementen kinderen met kanker EN tromboseprofylaxe. Zoals besproken is vanwege de grote opbrengst in eerste instantie alleen gezocht naar SR's en RCT's. → De sleutelartikelen PMID30262570 en PMID31600808 worden gevonden met deze search. De sleutelartikelen PMID35289066 en PMID29178421 vallen uit op studiedesign.	
Te gebruiken voor richtlijntekst: In de databases Embase.com en Ovid/Medline is op 7 maart 2024 systematisch gezocht naar systematische reviews en RCTs over tromboseprofylaxe bij kinderen met kanker. De literatuurzoekactie leverde 463 unieke treffers op.	

Zoekopbrengst 7-3-2024

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SR	290	47	295
RCT	159	40	168
Observationeel			
Totaal	449	87	**463***

***in Rayyan**

Zoekstrategie Embase.com 7-3-2024

No.	Query	Results
#1	'neoplasm'/exp OR adenoma*:ti,ab,kw OR anticarcinogen*:ti,ab,kw OR blastoma*:ti,ab,kw OR cancer*:ti,ab,kw OR carcinogen*:ti,ab,kw OR carcinom*:ti,ab,kw OR carcinosarcoma*:ti,ab,kw OR chordoma*:ti,ab,kw OR germinoma*:ti,ab,kw OR gonadoblastoma*:ti,ab,kw OR hepatoblastoma*:ti,ab,kw OR ((hodgkin* NEXT/1 disease):ti,ab,kw) OR leukemi*:ti,ab,kw OR lymphangioma*:ti,ab,kw OR lymphangiomyoma*:ti,ab,kw OR lymphangiosarcoma*:ti,ab,kw OR lymphom*:ti,ab,kw OR malignan*:ti,ab,kw OR melanom*:ti,ab,kw OR meningioma*:ti,ab,kw OR mesenchymoma*:ti,ab,kw OR mesonephroma*:ti,ab,kw OR metasta*:ti,ab,kw OR neoplas*:ti,ab,kw OR neuroma*:ti,ab,kw OR nsclc:ti,ab,kw OR oncogen*:ti,ab,kw OR oncolog*:ti,ab,kw OR paraneoplastic:ti,ab,kw OR plasmacytoma*:ti,ab,kw OR precancerous:ti,ab,kw OR sarcoma*:ti,ab,kw OR teratocarcinoma*:ti,ab,kw OR teratoma*:ti,ab,kw OR tumor*:ti,ab,kw OR tumour*:ti,ab,kw	7580970
#2	'adolescent'/exp OR 'baby'/exp OR 'boy'/exp OR 'child'/exp OR 'minors'/exp/mj OR 'pediatric patient'/exp OR 'pediatrics'/exp OR 'schoolchild'/exp OR infan*:ti,ab OR newborn*:ti,ab OR 'new born*':ti,ab OR perinat*:ti,ab OR neonat*:ti,ab OR baby*:ti,ab OR babies:ti,ab OR toddler*:ti,ab OR minors*:ti,ab OR boy:ti,ab OR boys:ti,ab OR boyfriend:ti,ab OR boyhood:ti,ab OR girl*:ti,ab OR kid:ti,ab OR kids:ti,ab OR child*:ti,ab OR children*:ti,ab OR schoolchild*:ti,ab OR adolescen*:ti,ab OR juvenil*:ti,ab OR youth*:ti,ab OR teen*:ti,ab OR pubescen*:ti,ab OR pediatric*:ti,ab OR paediatric*:ti,ab OR peadiatric*:ti,ab OR school:ti,ab OR school*:ti,ab OR prematur*:ti,ab OR preterm*:ti,ab	5899259
#3	'thrombosis prevention'/exp OR 'anticoagulant agent'/exp OR 'anticoagulation'/exp OR 'anticoagulant therapy'/exp OR 'low molecular weight heparin'/exp OR 'dalteparin'/exp OR 'enoxaparin'/exp OR 'nadroparin'/exp OR 'tinzaparin'/exp OR 'dabigatran'/exp OR 'rivaroxaban'/exp OR thromboprophyla*:ti,ab,kw OR ((thrombo* NEAR/3 (prophylaxis OR prophylactic OR prevention)):ti,ab,kw) OR 'anti coagulant*':ti,ab,kw OR 'anticoagulant*':ti,ab,kw OR 'anticoagulat*':ti,ab,kw OR 'anti coagulat*':ti,ab,kw OR 'antithrombotic*':ti,ab,kw OR 'anti thrombotic*':ti,ab,kw OR 'antithrombocytic*':ti,ab,kw OR 'anti thrombocytic*':ti,ab,kw OR 'antiplatelet agent*':ti,ab,kw OR 'antiplatelet drug*':ti,ab,kw OR 'platelet aggregation inhibitor*':ti,ab,kw OR 'platelet inhibitor*':ti,ab,kw OR 'platelet antagonist*':ti,ab,kw OR 'thrombocyte aggregation inhibiting	919483

	agent*':ti,ab,kw OR 'thrombocyte aggregation inhibitor*':ti,ab,kw OR 'direct oral anticoagulant agent'/exp OR 'direct oral anticoagulant'/exp OR doac*:ti,ab,kw OR 'low molecular heparin*':ti,ab,kw OR 'low molecular weight heparin*':ti,ab,kw OR 'dalteparin*':ti,ab,kw OR 'enoxaparin*':ti,ab,kw OR 'nadroparin*':ti,ab,kw OR 'tinzaparin':ti,ab,kw OR 'dabigatran':ti,ab,kw OR 'rivaroxaban':ti,ab,kw	
#4	#1 AND #2 AND #3	11094
#5	#4 AND [2013-2024]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	4026
#6	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	1007394
#7	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	2168142
#8	#5 AND #6 **– SR's**	290
#9	#5 AND #7 NOT #8 **– RCT's**	159
#10	#8 OR #9	449

Zoekstrategie Ovid/Medline 7-3-2024

#	Searches	Results
1	exp Neoplasms/ or adenoma*.ti,ab,kf. or anticarcinogen*.ti,ab,kf. or blastoma*.ti,ab,kf. or cancer*.ti,ab,kf. or carcinogen*.ti,ab,kf. or	5440300

	carcinom*.ti,ab,kf. or carcinosarcoma*.ti,ab,kf. or chordoma*.ti,ab,kf. or germinoma*.ti,ab,kf. or gonadoblastoma*.ti,ab,kf. or hepatoblastoma*.ti,ab,kf. or (hodgkin* adj1 disease).ti,ab,kf. or leukemi*.ti,ab,kf. or lymphangioma*.ti,ab,kf. or lymphangiomyoma*.ti,ab,kf. or lymphangiosarcoma*.ti,ab,kf. or lymphom*.ti,ab,kf. or malignan*.ti,ab,kf. or melanom*.ti,ab,kf. or meningioma*.ti,ab,kf. or mesenchymoma*.ti,ab,kf. or mesonephroma*.ti,ab,kf. or metasta*.ti,ab,kf. or neoplas*.ti,ab,kf. or neuroma*.ti,ab,kf. or nsclc.ti,ab,kf. or oncogen*.ti,ab,kf. or oncolog*.ti,ab,kf. or paraneoplastic.ti,ab,kf. or plasmacytoma*.ti,ab,kf. or precancerous.ti,ab,kf. or sarcoma*.ti,ab,kf. or teratocarcinoma*.ti,ab,kf. or teratoma*.ti,ab,kf. or tumor*.ti,ab,kf. or tumour*.ti,ab,kf.	
2	(child* or schoolchild* or infan* or adolescen* or pediatri* or paediatr* or neonat* or boy or boys or boyhood or girl or girls or girlhood or youth or youths or baby or babies or toddler* or childhood or teen or teens or teenager* or newborn* or postneonat* or postnat* or puberty or preschool* or suckling* or picu or nicu or juvenile?).tw.	3003438
3	exp Anticoagulants/ or exp Platelet Aggregation Inhibitors/ or thromboprophyla*.ti,ab,kf. or (thrombo* adj3 (prophylaxis or prophylactic or prevention)).ti,ab,kf. or (anti coagulant* or anticoagulant* or anticoagulat* or anti coagulat* or antithrombotic* or anti thrombotic* or antithrombocytic* or anti thrombocytic* or 'antiplatelet agent*' or 'antiplatelet drug*' or 'platelet aggregation inhibitor*' or 'platelet inhibitor*' or platelet antagonist* or 'thrombocyte aggregation inhibiting agent*' or 'thrombocyte aggregation inhibitor*' or doac*).ti,ab,kf.	439695
4	1 and 2 and 3	1398
5	limit 4 to yr="2013 -Current"	648
6	5 not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)	589
7	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	730635

8	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1694471
9	6 and 7 **– SR's**	47
10	(6 and 8) not 9 **– RCT's**	40
11	9 or 10	87

5

Module 5 Behandeling intermediair-hoog risico longembolie

Autorisatie en geldigheid

Autorisatiedatum:	*pending*
Eerstvolgende beoordeling actualiteit	volgende cyclus binnen het cluster Antitrombotisch beleid
Geautoriseerd door:	*pending*
Belangrijkste wijzigingen t.o.v. vorige versie:	n.v.t., het betreft een nieuwe module
Herbevestiging:	n.v.t.
Regiehouder:	Nederlandse Internisten Vereniging

Uitgangsvraag

Wat is de optimale behandeling van patiënten met acute intermediair-hoog risico longembolie?

Introduction

Acute intermediate-high risk pulmonary embolism compasses patients with acute PE who are hemodynamically stable but have a high early mortality risk. Early mortality of patients with acute intermediate-high risk pulmonary embolism (PE) is around 3%. Despite hemodynamic stability at the time of presentation, the risk of hemodynamic decompensation is around 4% in the first 48 hours after diagnosis (Meyer, 2014). According to the ESC-guidelines (Konstantinides, 2020), the first choice of treatment is initiation of anticoagulants and not rescue reperfusion therapy, i.e. systemic thrombolysis, percutaneous catheter-guided intervention (encompassing local thrombolysis, and/or fragmentation, and/or thrombus aspiration), or surgical embolectomy.

This patiënt group with acute intermediate-high risk PE is identified following the risk-adjusted management strategy of the ESC guidelines (Konstantinides, 2020). Risk stratification of patients with acute PE is recommended for determining the appropriate therapeutic management approach and begins upon suspicion of the disease and initiation of the diagnostic workup. This prognostic risk score combines clinical, imaging, and laboratory parameters to permit a (semi)quantitative assessment of early PE-related risk of death.

However the implications of this risk score for patient management in the acute setting in some domains is not always clear because of gaps in evidence. Also the severity of symptoms at time of clinical presentation in, the high early mortality rates, and uncertainties regarding long-term outcomes (including quality of life, post-pulmonary embolism syndrome, and chronic thromboembolic pulmonary hypertension), leads to variation in therapeutic management and sometimes the use of rescue reperfusion therapy. In daily clinical practice, this also leads to variation in how long and in what way these patients are monitored during admission in the hospital. Sometimes patients are admitted to a regular nursing ward and in other hospitals to an medium care or intensive care unit, with consequences for hospital capacity and costs. This latter subject is not the primary focus of this module.

Search and select

A systematic review of the literature was performed to answer the following question: What are the desirable and undesirable effects of systemic thrombolysis, percutaneous catheter-guided interventions, or surgical embolectomy in comparison with initiation of anticoagulation in patients with acute intermediate-high risk pulmonary embolism?

Table 1: PICO

Patients	Adult patients with acute intermediate-high risk pulmonary embolism *Defined by objectively demonstrated PE, right ventricular dysfunction on CTPA and/or echocardiogram, and increased troponin as defined by the ESC guidelines (Konstantinides, 2020)*
Intervention	Systemic thrombolysis (ST) Percutaneous catheter-guided intervention (CDI)* Surgical embolectomy (SE)
Control	Anticoagulation (any type)
Outcomes	• PE-related mortality • All-cause mortality • Hemodynamic deterioration • Bleeding complications • Recurrence of pulmonary embolism • Quality of life/PROMS • Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension
Other selection criteria	Study design: systematic reviews, randomized controlled trials and cohort studies (include at least 500 patients and adjusted for confounding (any type of analysis))

***CDI includes catheter-directed local thrombolysis with or without mechanical or ultrasound-assisted fragmentation or thrombus aspiration).**

Relevant outcome measures

The guideline development group considered PE-related mortality, all-cause mortality, hemodynamic deterioration, bleeding complications, and recurrence of pulmonary embolism as critical outcome measures for decision making; and quality of life/PROMS and chronic thrombo-embolic pulmonary hypertension (CTEPH) or chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension as important outcome measures for decision making.

A priori, the guideline panel did not use one definition for the patient population listed above. In the literature, different terms are used which can indicate intermediate-high risk PE patients, e.g. moderate or submassive PE. In the broadest terms, the population from the selected studies included hemodynamically stable patients with acute PE and signs of right ventricle dysfunction, irrespective of the term used to describe the population.

The working group defined a RD of 3%* as a minimal clinically (patient) important difference.

**Based on the differences applied in the guidelines on thromboprophylaxis in patients with COVID-19. This working group derived the minimal clinically (patient) important differences from the ACCP (2012).*

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 5 July 2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 520 hits. Studies were selected based on the following criteria:

- Original study published after 2000.
- Systematic review with a detailed search strategy and risk of bias assessment of the included studies.
- Randomized controlled trials.

- Cohort studies conform the PICO with at least 500 patients and adjustment for confounding (any type of analysis).

162 studies were initially selected based on title and abstract screening. After reading the full text, 161 studies were excluded (see the table with reasons for exclusion under the tab Methods), and one study was included.

A systematic review and network meta-analysis by Planer (Planer, 2023) was included. This review included RCTs, observational cohort and case-control studies comparing catheter-directed thrombolysis (CDT) with or without mechanical or ultrasound-assisted fragmentation with other therapeutic options including anticoagulation and systemic thrombolysis (ST). Small cohort studies without adjustment for confounding were also included in this systematic review. Planer and colleagues excluded 8 observational studies based on high risk of bias. These selection criteria were different than the selection criteria for this PICO. Because the search strategy used by Planer (2023) was adequate, we decided to review the included and excluded observational studies. The final selection of the reviewed studies by Planer (2023) to answer this PICO, can be found in the table with reasons for exclusion. Of the total of 44 studies included by Planer (2023), 8 RCTs and 7 cohort studies were finally included in our analyses. No RCTs investigating surgical embolectomy were found.

Results

15 studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Planer and colleagues (Planer, 2023) undertook a systematic review into therapeutic options for patients with intermediate or high-risk PE. Anticoagulation, ST, and CDT were considered as treatment options. The authors searched multiple databases from inception to 18 October 2022. RCTs, cohort studies, and case-control studies were included if patients presented with intermediate or high-risk PE and a comparison between the stated treatment options was made.

Of the total of 44 studies included by Planer (Planer, 2023), a total of 8 RCTs and 7 cohort studies were included in our literature analysis (Table 2). The majority of studies were excluded because of a publication date before 2000 or a sample size smaller than 500 for cohort studies. An overview of the characteristics of the included studies is given in Table 2. Studpopuations of these studies contains at least partially acute intermediate high-risk PE patients. Although not explicitly stated in some cohort studies, it is assumed that CDT or ST is always followed by the initiation of AC.

Table 2: Overview of included studies from Planer (2023)

Author, year	N[a]	Intervention	Comparator	Follow-up
RCT				
Kroupa, 2022	23	CDT + AC	AC	30 days
Sadeghipour, 2022	94	CDT + AC	AC	3 months
Zhang, 2018[b]	66	ST (low dose) + AC	AC	3 months after discharge
Kucher, 2014	59	CDT (USAT) + AC	AC (UFH)	3 months after discharge
Meyer, 2014	1005	ST + AC	AC	30 days

Sharifi, 2013[b]	121	ST (low dose) + AC	AC	28 months
Fasullo, 2011	72	ST + AC	AC	6 months
Konstantinides, 2002	256	ST + AC	AC (UFH)	30 days[c]
Cohort study[d]				
Krishnan, 2022	13.325	CDT + AC	ST + AC or AC	Unclear
Hobohm, 2021	> 40000	CDT + AC	ST + AC or AC	Unclear
Lin, 2021	1303	CDT + AC	ST	> 3 years
Stein, 2020	6340	CDT + AC	AC	Unclear
Arora, 2017	3384	CDT + AC	ST + AC	Unclear
Patel, 2015	Unmatched: 1521	CDT + AC	ST + AC	Unclear

AC, anticoagulation; CDT, catheter-directed thrombolysis; ST, systemic thrombolysis; USAT, Ultrasound-accelerated thrombolysis; UFH, unfractionated heparine
a. Total number of included patients; for cohort studies, the number of matched participant if applicable.
b. These studies used a low-dose ST. The meta-analyses showed no inconsistency potentially caused by low-dose ST. Therefore, no separate analyse on dosage was performed.
c. Not reported but deduced from figure in paper.
d. In this sudies ICD codes were used to determine use of CDT; frequently groups with ultrasound assistance and without were analyzed together.

Results

PE-related mortality

Only the RCTs reported data on PE-related mortality. The result of the meta-analysis is shown in Figure 3.

CDT + AC versus AC

Three RCTs compared CDT + AC with AC. Two RCTs reported no deaths due to PE. The one remaining RCT saw no deaths due to PE in the intervention group and two deaths in the control group. Because of the low number of deaths, no conclusion could be drawn.

ST + AC versus AC

Two RCTs compared ST + AC versus AC. The RCTs saw no deaths due to PE in the intervention group. The total of seven deaths due to PE were all in the group which received only anticoagulation. The low number of events results in effect estimate with very broad confidence intervals. It is therefore difficult to conclude anything of the interventions on the outcome PE-related mortality.

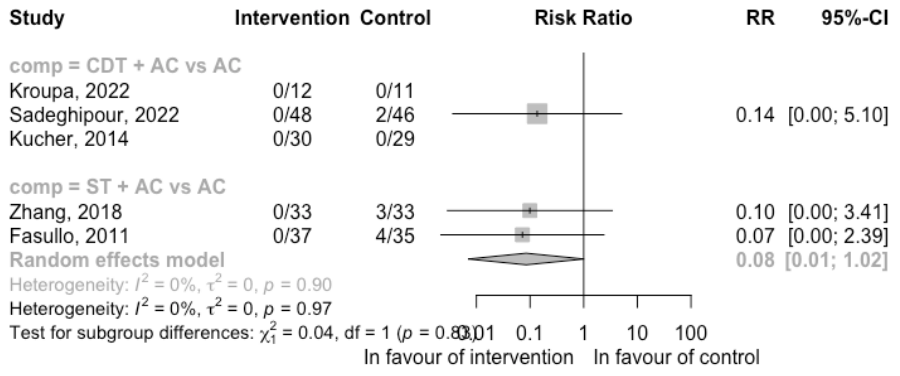


Figure 3: Meta-analysis of RCTs for the outcome PE mortality
ST, systemic thrombolysis; CDT, catheter-directed thrombolysis; AC, anticoagulation

All-cause mortality

The results of the meta-analysis per comparisons for the outcome all-cause mortality is shown in Figure 4 for the RCTs and in Figure 5 for cohort studies.

CDT + AC versus (ST +) AC

Three RCTs compared CDT + AC with AC (Figure 4). One RCT reported no death. The remaining RCTs saw no deaths in the intervention group and four deaths in the control group. Because of the low number of deaths, no conclusion could be drawn.

Three cohort studies, comparing CDT + AC with AC, reported a reduced risk of mortality (RR 0.51 95%CI 0.40 to 0.63) (Figure 5). A similar reduced risk was observed for the comparison with ST + AC (RR 0.46 95%CI 0.38 to 0.56). Included cohortstudies were registry-based studies with problems with the intervention assessment and confounding by indication resulting in a high risk of bias. Therefore, no conclusion could be drawn regarding the outcome all-cause mortality.

ST + AC versus AC

Four RCTs compared ST + AC versus AC (Figure 4). There is an indication that the risk of death is reduced with ST + AC versus AC (RR 0.67 95%CI 0.31 to 1.45). However, the confidence interval is broad.

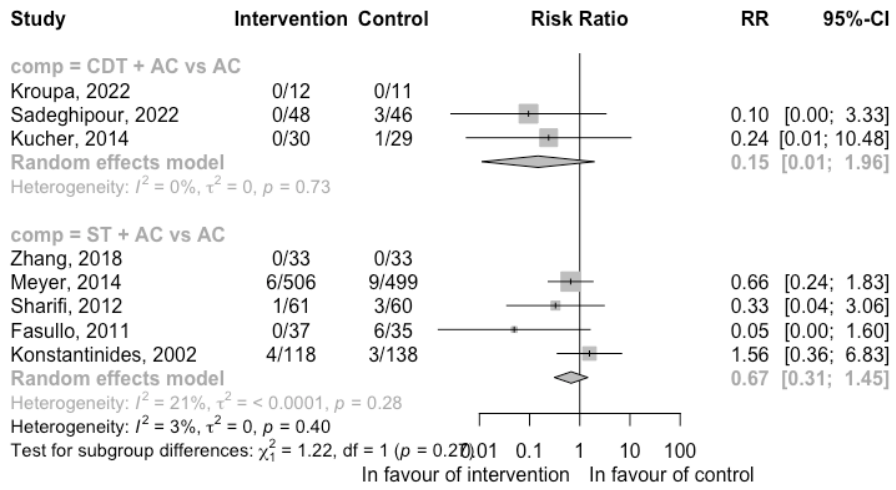


Figure 4: Meta-analysis of RCTs for the outcome all-cause mortality

ST, systemic thrombolysis; CDT, catheter-directed thrombolysis; AC, anticoagulation

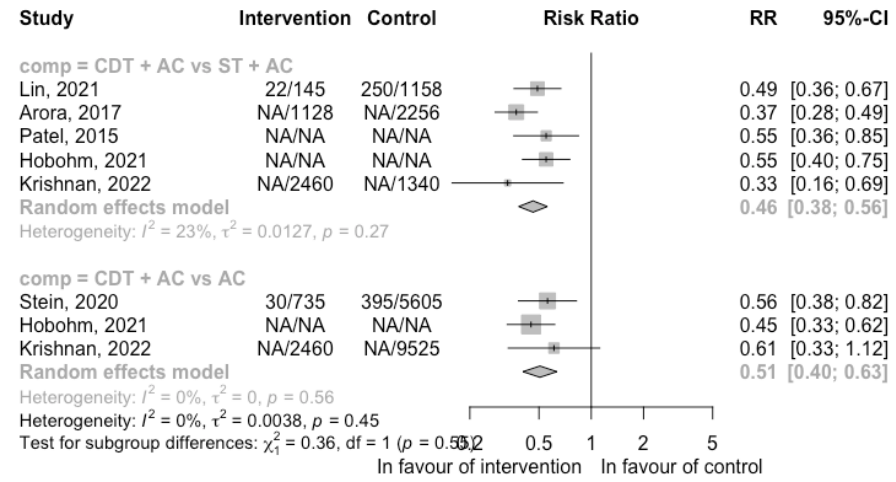


Figure 5: Meta-analysis of cohort studies for the outcome all-cause mortality

ST, systemic thrombolysis; CDT, catheter-directed thrombolysis; AC, anticoagulation; NA, not reported in the original article.

Hemodynamic deterioration

CDT + AC versus AC

Three RCTs reported on the outcome hemodynamic deterioration (Figure 6). Only one RCT reported one hemodynamic instability despite treatment with vasopressor agent (Sadeghipour, 2022). Because of the low number of events, no conclusion could be drawn.

ST + AC versus AC

One RCT reported events of hemodynamic decompensation (Meyer, 2014; Figure 6) comparing ST + AC with AC. A reduced risk of hemodynamic deterioration is observed with ST + AC versus AC (RR 0.32 95%CI 0.14 to 0.69).

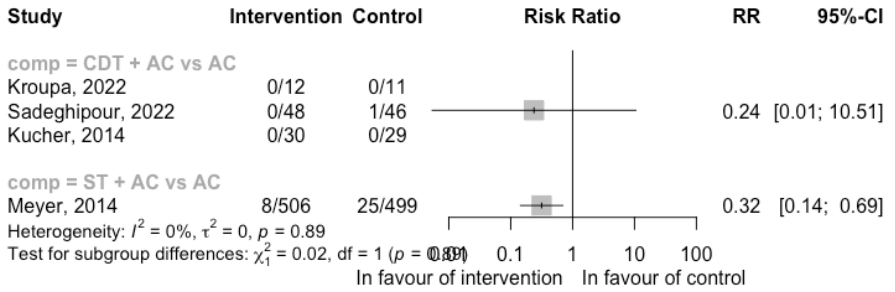


Figure 6: Meta-analysis of RCTs for the outcome hemodynamic deterioration
ST, systemic thrombolysis; CDT, catheter-directed thrombolysis; AC, anticoagulation

Bleeding complications

Major bleeding events

CDT + AC versus (ST +) AC

Three RCTs comparing CDT + AC with AC reported on the outcome major bleedings (Figure 7). Only one RCT reported one major bleeding event in the intervention group (Sadeghipour, 2022). Because of the low number of events, no conclusion could be drawn.

One cohort study compared CDT + AC with ST + AC (Figure 8). The risk of a major bleeding event was similar between the groups (RR 1.02 95%CI 0.75 to 1.38). The included cohortstudy was registry based with problems with the intervention assessment and confounding by indication resulting in a high risk of bias.

ST + AC versus AC

Four RCTs reported major bleeding events (Figure 7 & 8) comparing ST + AC with AC. The results from the RCTs are inconsistent. The largest RCT reported an increased risk; however, the other two RCTs with a low number of events (n ≤ 5) indicated an increased risk or a reducted risk both with broad confidence intervals.

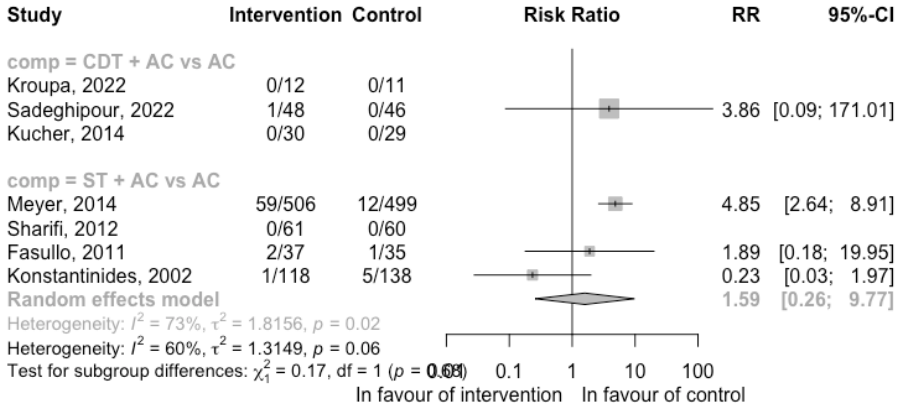


Figure 7: Meta-analysis of RCTs for the outcome major bleeding events
ST, systemic thrombolysis; CDT, catheter-directed thrombolysis; AC, anticoagulation

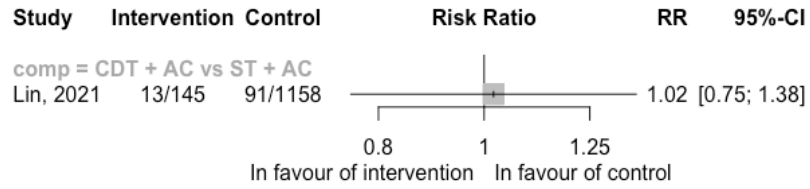


Figure 8: Meta-analysis of cohort studies for the outcome major bleeding events
ST, systemic thrombolysis; CDT, catheter-directed thrombolysis; AC, anticoagulation

Minor bleeding events

CDT + AC versus AC

Three RCTs reported on the outcome minor bleedings (Figure 9). The RCTs suggest a potential increased risk of minor bleeding events for CDT + AC (RR 1.73 95%CI 0.34 to 8.72); however, the number of events is low (in total n ≤ 10).

ST + AC versus AC

Four RCTs reported events on minor bleeding events (Figure 9) comparing ST + AC with AC. A increased risk of minor bleeding events is observed with ST + AC versus AC (RR 3.66 95%CI 1.82 to 7.36).

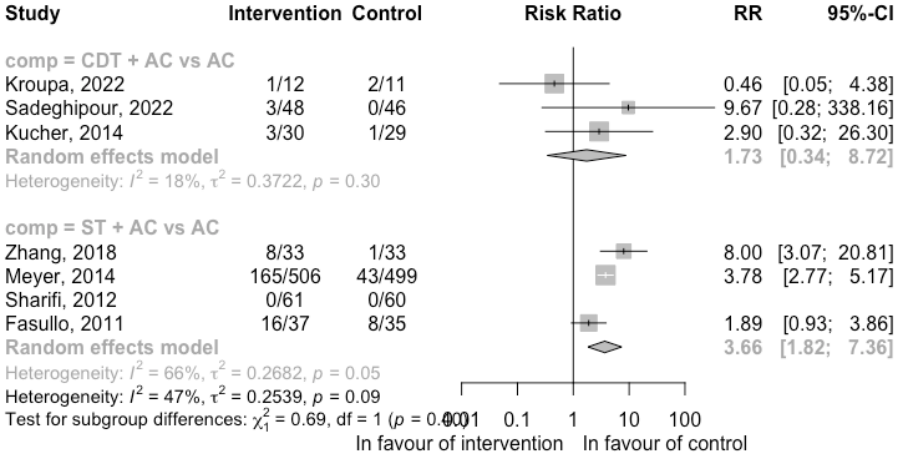


Figure 9: Meta-analysis of RCTS for the outcome minor bleeding events
ST, systemic thrombolysis; CDT, catheter-directed thrombolysis; AC, anticoagulation

Recurrence of pulmonary embolism

CDT + AC versus ST + AC

No RCTs reported the outcome of a recurrence. One cohort study reported on the comparison CDT + AC versus ST + AC (Figure 11). The risk of a recurrence is reduced with CDT + AC versus ST + AC (RR 0.84 95%CI 0.72 to 0.98). The cohort study was a registry-based study with problems with the intervention assessment and confounding by indication resulting in a high risk of bias.

ST +AC versus AC

Four RCTs comparing ST + AC with AC reported data on a recurrence of PE (Figure 10). There may be a reduced risk of a recurrence with ST + AC compared with AC (RR 0.51 95%CI 0.17 to 1.59); however, the confidence interval is broad suggesting potentially a decreased risk, no risk or increased risk.

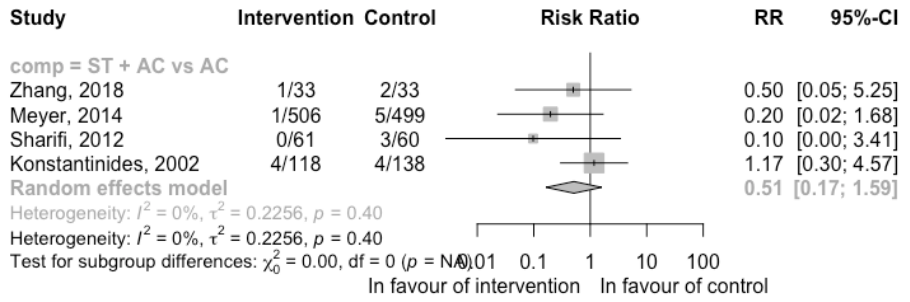


Figure 10 Meta-analysis of RCTs for the outcome recurrence of pulmonary embolism
ST, systemic thrombolysis; CDT, catheter-directed thrombolysis; AC, anticoagulation

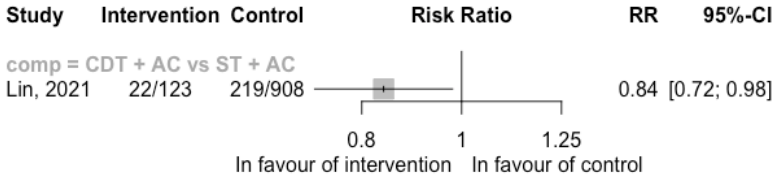


Figure 11: Meta-analysis of cohort studies for the outcome recurrence of pulmonary embolism
ST, systemic thrombolysis; CDT, catheter-directed thrombolysis; AC, anticoagulation

Quality of life/PROMS

None of the included studies reported any results on quality of life or PROMS.

Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension

None of the included studies reported any results on this outcome.

Level of evidence of the literature

PE-related mortality

The level of evidence starts at high as RCTs reported on this outcome. The level of evidence was downgraded by three levels to very low because of imprecision (very broad confidence interval).

All-cause mortality

The level of evidence is assessed separately for each study design. As the assessment of the level of evidence was the same per comparison, no distinction between the comparions was made.

- RCTs: the level of evidence starts at high and was downgraded by three levels to very low because of imprecision (very broad confidence interval).
- Cohort studies: The level of evidence starts at low for observational studies for the domain intervention. Risk of bias assessment of the cohortstudies showed issues with the intervention definition and confounding by indication. Therefore, we further downgraded from low to very low due to risk of bias.

Hemodynamic deterioration

The level of evidence starts at high as RCTs reported on this outcome.

- The level of evidence was downgraded by three levels for the comparison *CDT+ AC versus AC*, because of imprecision (very broad confidence interval).
- The level of evidence was not downgraded for the comparison *ST + AC versus AC*. Although the number of events was low, the sample size (N > 337 per arm) was sufficient to detect an effect.

Bleeding complications

Major bleeding:

- Because of the low number of events, the level of evidence for the comparison *CDT + AC versus AC* was not assessed.
- The level of evidence starts at low as cohort studies reported for this outcome and the comparison *CDT + AC versus ST + AC*. Risk of bias assessment of the cohortstudies showed issues with the intervention definition and confounding by indication. Therefore, we further downgraded from low to very low due to risk of bias.
- The level of evidence starts at high as RCTs reported for this outcome and comparison. The level of evidence was downgraded by three levels for the comparison *ST + AC versus AC*, because of imprecision (confidence interval crosses both boundaries of minimal important difference).

Minor bleeding:

The level of evidence starts at high as RCTs reported on this outcome.

- The level of evidence was downgraded by three levels for the comparison *CDT+ AC versus AC*, because of imprecision (very broad confidence interval).
- The level of evidence was not downgraded for the comparison *ST + AC versus AC*. The sample size (N > 98 per arm) was sufficient to detect an effect.

Recurrence of pulmonary embolism

- The level of evidence starts at high as RCTs reported for this outcome and the comparison *ST + AC versus AC*. The level of evidence was downgraded by three levels, because of inconsistency (one level) and imprecision (confidence interval crosses both boundaries of minimal important difference).
- The level of evidence starts at low as cohort studies reported for this outcome and the comparison *CDT + AC versus ST + AC*. The level of evidence was downgraded by one level from low to very low, because of imprecision (confidence interval crosses one boundary of minimal important difference) and risk of bias (issues with the intervention definition and confounding by indication).

Conclusions

PE-related mortality

Very low GRADE	The evidence is very uncertain about the effect of CDT or ST on PE-related mortality when compared with AC in patients with acute intermediate-high risk PE. *Source: Kroupa, 2022; Sadeghipour, 2022; Zhang, 2018; Kucher, 2014; Fasullo, 2011*

All-cause mortality

Very low GRADE	The evidence is very uncertain about the effect of CDT or ST on all-cause mortality when compared with AC in patients with acute intermediate-high risk PE. *Source: Kroupa, 2022; Sadeghipour, 2022; Kucher, 2014; Zhang, 2018; Meyer, 2014; Sharifi, 2012; Fasullo, 2011; Konstantinides, 2002; Krishnan, 2022; Hobohm, 2021; Lin, 2021; Stein, 2020; Arora, 2017; Patel, 2015*

Hemodynamic deterioration

Very low GRADE	*CDT + AC vs AC* The evidence is very uncertain about the effect of CDT + AC on hemodynamic deterioration when compared with AC in patients with acute intermediate-high risk PE. *Source: Sadeghipour, 2022*
High GRADE	*ST + AC vs AC* ST + AC reduces the risk of hemodynamic deterioration when compared with AC in patient with acute intermediate-high risk PE. *Source: Meyer, 2014*

Bleeding complications

Very low GRADE	*Major bleeding events* The evidence is very uncertain about the effect of CDT or ST on major bleedings when compared with AC in patients with acute intermediate-high risk PE. *Source: Kroupa, 2022; Sadeghipour, 2022; Lin, 2021; Kucher, 2014; Meyer, 2014; Sharifi, 2012; Fasullo, 2011; Konstantinides, 2002*
Very low GRADE	*Minor bleeding events* *CDT + AC vs AC* The evidence is very uncertain about the effect of CDT + AC on minor bleeding events when compared with AC in patients with acute intermediate-high risk PE. *Source: Kroupa, 2022; Sadeghipour, 2022; Kucher, 2014*
High GRADE	*ST + AC vs AC* ST + AC increases the risk of minor bleeding events when compared with AC in patient with acute intermediate-high risk PE. *Source: Zhang, 2018; Meyer, 2014; Sharifi, 2012; Fasullo, 2011*

Recurrence of pulmonary embolism

Very low GRADE	*ST + AC vs AC* The evidence is very uncertain about the effect of ST + AC on recurrence of pulmonary embolism when compared with AC in patients with acute intermediate-high risk PE. *Source: Zhang, 2018; Meyer, 2014; Sharifi, 2012; Konstantinides, 2002* *CDT + AC vs ST + AC* The evidence is very uncertain about the effect of CDT + AC on recurrence of pulmonary embolism when compared with ST + AC in patients with acute intermediate-high risk PE. *Source: Lin, 2021*

5

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Voor deze module is een literatuuranalyse gedaan naar de effectiviteit en veiligheid van systemische trombolyse, percutane katheter-geleide interventies en chirurgische embolectomie in vergelijking met het initiëren van therapeutische antistolling bij patiënten met een acute intermediar-hoog risico longembolie. De bewijskracht voor de cruciale uitkomstmaten (longembolie-gerelateerde mortaliteit, all-cause mortaliteit, hemodynamische verslechtering, bloedingscomplicaties en recidief longembolie) varieerde van hoog tot zeer laag. Voor de literatuuranalyse hebben we gekozen om naast RCT's ook cohortstudies te includeren. Bij het selecteren van de studies zijn we streng geweest door alleen studies mee te nemen die van voldoende grootte waren en correctie voor confounding hadden toegepast. Echter, de cohortstudies zijn allen registrystudies met de nodige methodologische tekortkomingen. De bepaling van de interventie was bij de studies onzeker (gebaseerd op ICD-codes of declaraties zonder een check of dit klopte) en ook confounding by indication speelde een grote rol.

Ondanks dat een van de grootste RCT's, de PEITHO-trial (Meyer, 2014), aantoont dat systemische thrombolyse het risico op hemodyamische decompensatie verminderd in patienten met intermediar-hoog risico longembolie (bewijskracht hoog), adviseert de werkgroep dit niet als standaard behandeling. Dit omdat in deze zelfde studie een sterkverhoogd risico op ernstige bloedingen gezien werd , met name cerebrale bloedingen in de oudere populatie (>65 jaar).

Ook moet de conclusie en bewijskracht over mineure bloedingen in perspectief geplaatst worden. De bewijskracht en conclusie wordt vooral gedreven door de resultaten uit deze PEITHO-trial van Meyer en collegae (Meyer, 2014). Echter, een mineure bloeding heeft geen eenduidige definitie. Daarom is het lastig een gegeneraliseerde conclusie te trekken gebaseerd op alle studies.

Er is geen geschikte relevante literatuur over chirurgische embolectomie en dit maakt dat de werkgroep geen uitspraak kan doen over de effectiviteit en veligheid van een chirurgische embolectomie in deze patientengroep.

Vanwege deze onzekerheden in de literatuur adviseert de werkgroep om patiënten met een acute intermediair-hoog risico longembolie bij initiële presentatie te behandelen met alleen anticoagulantia.

Anticoagulantia

Rescue reperfusie therapie, te weten systemische trombolyse (volle en gereduceerde dosis), percutane katheter-geleide interventies en chirurgische embolectomie, moeten worden gereserveerd voor patiënten met een intermediair-hoog risico longembolie, die hemodynamische instabiliteit ontwikkelen. In de PEITHO-trial (Meyer, 2014) was de gemiddelde tijd tussen randomisatie en overlijden of hemodynamisch decompensatie 1,79 $\pm$ 1,60 dagen in de placebo (alleen heparine) arm. Daarom lijkt het redelijk om patiënten met een acute intermediair-hoog risico longembolie gedurende de eerste 2-3 dagen met LMWH te behandelen, en nadat een patient gestabiliseerd is, na deze initiële periode pas over te stappen op orale antistolling. Het is minder wenselijk om deze patienten initieel met orale antistolling, zoals DOAC's te behandelen, vanwege de verhoogde kans op escalatie van de therapie, waaronder systemsiche thrombolyse, en daarmee potentiele bloedingscomplicaties. De werkgroep adviseert bij patiënten met een acute intermediair-hoog risico longembolie te starten met LMWH gezien de kans op hemodynamische verslechtering en mogelijke escalatie naar rescue reperfusie therapie.

Patiënten met een acute intermediair-hoog risico longembolie bij wie therapeutische antistolling wordt geïnitieerd, dienen gecontroleerd te worden op therapie succes dan wel therapie falen. In het geval van therapiefalen is er sprake van progressief

rechterventrikelfalen, zich uitend in hemodynamische verslechtering of circulatoire collaps, of het persisteren van rechterventrikeldysfunctie met bijbehorende kliniek onder adequate therapeutische antistolling. Er zijn geen eenduidige definities beschikbaar van therapie succes dan wel falen. De werkgroep sluit zich aan bij de volgende voorgestelde definities (Pruszczyk, 2022):

1. Therapiesucces: De initiële behandeling resulteert in de verbetering van de aanvankelijk gecompromitteerde hemodynamische status: een verlaging van de hartslag en ademhalingsfrequentie, verbetering van de systemische bloeddruk, zuurstofsaturatie en verbetering van de perifere perfusie. In dit scenario is geen escalatie van de therapie vereist.
2. Therapiefalen: Er is geen verbetering van de vitale parameters na 24-48 uur adequate therapeutische antistolling dan wel hemodynamische verslechtering en of circulatoire collaps. Als de patiënt na het starten van de behandeling met anticoagulantia hemodynamische instabiliteit ontwikkelt waarvoor vasopressie, reanimatie of ECMO (Extra Corporale Membraan Oxygenatie) noodzakelijk is, is er een duidelijke indicatie voor escalatie van therapie. Verslechtering bij aanvankelijk hemodynamisch stabiele PE-patiënten kan zich ook kenmerken door een progressieve tachycardie of ademhalingsfrequentie, daling van de systemische bloeddruk of zuurstofsaturatie, of door tekenen van orgaanhypoperfusie (afname van de urineproductie, stijging van het lactaat) gedurende ten minste 15 minuten, zonder te voldoen aan de officiële criteria van shock.

In het geval van therapiefalen dient reperfusietherapie in de vorm systemische trombolyse, percutane katheter-geleide interventies dan wel chirurgische embolectomie overwogen te worden.

In het geval van absolute of relatieve contra-indicaties voor therapeutische antistolling of systemische thrombolyse kunnen katheter-geleide interventies dan wel chirurgische embolectomie overwogen worden. De therapeutische interventie van voorkeur, de te verwachten winst en risico's, dienen per patiënt op individuele basis afgewogen te worden. Indien in het ziekenhuis een multidisciplinair EXPERT-PE-team aanwezig is, lijkt het rationeel om deze beslissing te nemen binnen dit team (Huisman, 2017).

Monitoring

Internationale richtlijnen (Konstantinides, 2020) adviseren dat patiënten met acute intermediair-hoog risico longembolieën gedurende de eerste uren tot dagen gemonitord moeten worden gezien het risico op vroege hemodynamische decompensatie. Er worden geen uitspraken gedaan over de duur van monitoring, wat deze monitoring inhoudt (welke parameters vervolgt moeten worden) en waar deze idealiter plaatsvindt. De werkgroep heeft in het kader van een SSC Subcommittee Project/Collaborative Project, genaamd Standardized risk stratification of acute pulmonary embolism, een literatuur search verricht (zie bijlage bij deze module (onder Zoekstrategie)) en geen geschikte literatuur geïdentificeerd om hierover een aanbeveling te kunnen doen. De werkgroep kan daarom geen aanbevelingen doen over de soort en duur van monitoring van patiënten met acute intermediair-hoog risico longembolieën. Ook kan de werkgroep daarom geen uistpraak doen of monitoring op een bewaakte afdeling voor deze patiënten nut heeft.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers).</u>

Er werd aandacht besteed aan het patiëntenperspectief door in de literatuur search kwaliteit van leven en PROMS mee te nemen. Er waren echter geen studies beschikbaar die deze uitkomstmaten hadden gerapporteerd.

Het patiëntenperspectief bij de behandeling van antistolling versus trombolyse voor acute longembolie is van cruciaal belang. Antistolling kan voor sommige patiënten een minder invasieve en minder riskante behandelingsoptie zijn met mogelijk minder bijwerkingen. Aan

de andere kant is systemsiche trombolyse snel en effectief bij een acuut potentieel levensgevaarlijke situatie, maar brengt het ook potentiele bloedingsrisico's met zich mee. Het patiëntenperspectief kan variëren afhankelijk van factoren zoals de ernst van de symptomen, reeds bestaande andere gezondheidsproblemen, risico's en bijwerkingen van de behandeling, en persoonlijke voorkeuren. Het is belangrijk om dit met de patient te bespreken en samen tot een passende behandeling te komen.

Kosten (middelenbeslag)

Het gebruik van anticoagulantia, zoals beschreven in deze module, brengt geen of nauwelijks gevolgen met zich mee voor de zorgkosten. De kosten voor rescue reperfusietherapie zijn hoger vanwege de prijs van de trombolyse medicatie en materiaalkosten van de katheters. Perlroth (2007) heeft een analyse verricht waaruit blijkt dat trombolyse kosteneffectief kan zijn voor een selecte subgroep hemodynamisch stabiele patienten met een intermediair hoog risico longembolie, waarbij het risico van overlijden hoog is.

Aanvaardbaarheid, haalbaarheid en implementatie

In de verschillende fasen van de richtlijnontwikkeling is rekening gehouden met de implementatie van de richtlijn (module) en de praktische uitvoerbaarheid van de aanbevelingen. De aanbevelingen zullen de huidige klinische praktijk zodanig weinig veranderen dat er geen problemen voorzien zijn in aanvaardbaarheid, haalbaarheid en er geen separaat implementatieplan is ontwikkeld. Het initiëren van rescue reperfusie therapie zal mogelijk meer en langdurige opnamecapaciteit van de ziekenhuizen vragen.

Aanbevelingen

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

De werkgroep is van mening dat momenteel patiënten met acute intermediair-hoog risico longembolie alleen behandeld dienen te worden met therapeutische antistolling. Huidige studies leveren onvoldoende bewijskracht om systemische thrombolyse, percutane katheter-geleide interventies en chirurgische embolectomie aan te kunnen bevelen in deze patiëntengroep. Studies tonen geen eenduidige verlaging van de longembolie gerelateerde mortaliteit, terwijl het effect op de bloedingscomplicaties onzeker is. Op basis van de huidige beschikbare literatuur kan de werkgroep geen uitspraak doen over het effect van systemische trombolyse en percutane katheter-geleide interventies op recidief longembolieën, kwaliteit van leven en het voorkomen van CTEPH/CTEPD zonder PH op de langere termijn. In de afweging van de aanbeveling zijn ook belasting van de ziekenhuiscapaciteit en kosten meegenomen.

Behandel patiënten met een acute intermediair-hoog risico longembolie bij initiële presentatie alleen met anticoagulantia. Start bij voorkeur met LMWH vanwege later mogelijke rescue reperfusietherapie bij therapiefalen.

Voor het inzetten van rescue reperfusietherapie bij therapiefalen verwijst de werkgroep naar de overwegingen.

Kennisvragen

Wat is het effect van CDT plus AC versus CDT alleen bij acute intermediair-hoog risico PE patienten? Hierbij missen er gerandomiseerde studies.

Wat is de optimale soort en duur van monitoring van patiënten met een acute intermediair-hoog risico longembolie? Heeft monitoring op een bewaakte afdeling voor deze patiënten nut?

Literatuur

Fasullo S, Scalzo S, Maringhini G, Ganci F, Cannizzaro S, Basile I, Cangemi D, Terrazzino G, Parrinello G, Sarullo FM, Baglini R, Paterna S, Di Pasquale P. Six-month echocardiographic study in patients with submassive pulmonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. Am J Med Sci. 2011 Jan;341(1):33-9.

Huisman MV, Montero Cabezas JM, Klok FA. Longembolie-interventieteams [Pulmonary embolism response teams: what is the added value for patients with acute pulmonary embolism?]. Ned Tijdschr Geneeskd. 2017;161:D1570. Dutch. PMID: 28831930.

Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W; Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med. 2002 Oct 10;347(15):1143-50.

Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ní Áinle F, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020 Jan 21;41(4):543-603.

Kroupa J, Buk M, Weichet J, Malikova H, Bartova L, Linkova H, Ionita O, Kozel M, Motovska Z, Kocka V. A pilot randomised trial of catheter-directed thrombolysis or standard anticoagulation for patients with intermediate-high risk acute pulmonary embolism. EuroIntervention. 2022 Oct 7;18(8):e639-e646.

Kucher N, Boekstegers P, Müller OJ, Kupatt C, Beyer-Westendorf J, Heitzer T, Tebbe U, Horstkotte J, Müller R, Blessing E, Greif M, Lange P, Hoffmann RT, Werth S, Barmeyer A, Härtel D, Grünwald H, Empen K, Baumgartner I. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014 Jan 28;129(4):479-86.

Lin DS, Lin YS, Wu CK, Lin HH, Lee JK. Midterm Prognosis of Patients With Pulmonary Embolism Receiving Catheter-Directed Thrombolysis or Systemic Thrombolysis: A Nationwide Population-Based Study. J Am Heart Assoc. 2021 Apr 6;10(7):e019296.

Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, Bluhmki E, Bouvaist H, Brenner B, Couturaud F, Dellas C, Empen K, Franca A, Galiè N, Geibel A, Goldhaber SZ, Jimenez D, Kozak M, Kupatt C, Kucher N, Lang IM, Lankeit M, Meneveau N, Pacouret G, Palazzini M, Petris A, Pruszczyk P, Rugolotto M, Salvi A, Schellong S, Sebbane M, Sobkowicz B, Stefanovic BS, Thiele H, Torbicki A, Verschuren F, Konstantinides SV; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014 Apr 10;370(15):1402-11.

Perlroth DJ, Sanders GD, Gould MK. Effectiveness and cost-effectiveness of thrombolysis in submassive pulmonary embolism. Arch Intern Med. 2007 Jan 8;167(1):74-80. doi: 10.1001/archinte.167.1.74. PMID: 17210881.

Planer D, Yanko S, Matok I, Paltiel O, Zmiro R, Rotshild V, Amir O, Elbaz-Greener G, Raccah BH. Catheter-directed thrombolysis compared with systemic thrombolysis and anticoagulation in patients with intermediate- or high-risk pulmonary embolism: systematic review and network meta-analysis. CMAJ. 2023 Jun 19;195(24):E833-E843.

Pruszczyk P, Klok FA, Kucher N, Roik M, Meneveau N, Sharp ASP, Nielsen-Kudsk JE, Obradović S, Barco S, Giannini F, Stefanini G, Tarantini G, Konstantinides S, Dudek D. Percutaneous treatment options for acute pulmonary embolism: a clinical consensus statement by the ESC Working Group on Pulmonary Circulation and Right Ventricular

Function and the European Association of Percutaneous Cardiovascular Interventions. EuroIntervention. 2022 Oct 7;18(8):e623-e638.

Sadeghipour P, Jenab Y, Moosavi J, Hosseini K, Mohebbi B, Hosseinsabet A, Chatterjee S, Pouraliakbar H, Shirani S, Shishehbor MH, Alizadehasl A, Farrashi M, Rezvani MA, Rafiee F, Jalali A, Rashedi S, Shafe O, Giri J, Monreal M, Jimenez D, Lang I, Maleki M, Goldhaber SZ, Krumholz HM, Piazza G, Bikdeli B. Catheter-Directed Thrombolysis vs Anticoagulation in Patients With Acute Intermediate-High-risk Pulmonary Embolism: The CANARY Randomized Clinical Trial. JAMA Cardiol. 2022 Dec 1;7(12):1189-1197.Sharifi M, Awdisho A, Schroeder B, Jiménez J, Iyer P, Bay C. Retrospective comparison of ultrasound facilitated catheter-directed thrombolysis and systemically administered half-dose thrombolysis in treatment of pulmonary embolism. Vasc Med. 2019 Apr;24(2):103-109.

Bijlagen bij module Behandeling van acute intermediair-hoog risico longembolie

Implementatietabel

5 Verkeerslichtanalyse

15

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	**Sterkte van de aanbeveling**	**Bewijskracht per uitkomstmaat**	**Verkeerslicht per (sub)aanbeveling**
Behandel patiënten met een acute intermediair-hoog risico longembolie bij initiële presentatie alleen met anticoagulantia. Start bij voorkeur met LMWH vanwege later mogelijke rescue reperfusietherapie bij therapiefalen. *Voor het inzetten van rescue reperfusietherapie bij therapiefalen verwijst de werkgroep naar de overwegingen.*	**X** Sterk (doe/ gebruik) / □ Zwak (overweeg)	**Overall bewijskracht** □ **H** □ **M** □ **L** **X VL** □ **NG** **Range bewijskracht van alle uitkomstmaten** **X H** □ **M** □ **L** **X VL** □ **NG** **OF** □ **voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in □ **ORANJE:** gebruik tabel B **X LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in

Implementatietabel

(De-)Implementatietabel met impuls analyse

Aanbeveling	Behandel patiënten met een acute intermediair-hoog risico longembolie bij initiële presentatie alleen met anticoagulantia. Start bij voorkeur met LMWH vanwege later mogelijke rescue reperfusietherapie bij therapiefalen. *Voor het inzetten van rescue reperfusietherapie bij therapiefalen verwijst de werkgroep naar de overwegingen.*
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**X Ongewenste praktijkvariatie** **□ Nieuwe evidentie** **□ Anders** **Toelichting:** De vroege mortaliteit van patiënten met een acute longembolie met een intermediair-hoog risico bedraagt ongeveer 3%. Ondanks hemodynamische stabiliteit op het moment van presentatie, bedraagt het risico op hemodynamische decompensatie ongeveer 4% in de eerste 48 uur na de diagnose (Meyer, 2014). Volgens de ESC-richtlijnen (Konstantinides, 2020) is de eerste keuze van de behandeling het starten van anticoagulantia en niet rescue reperfusietherapie, d.w.z. systemische trombolyse, percutane kathetergeleide interventie (inclusief lokale trombolyse en/of fragmentatie en/of trombusoperaties). aspiratie), of chirurgische embolectomie. Deze patiëntengroep met een acute intermediair-hoog risico longembolie wordt geïdentificeerd volgens de risicostratificatie van de ESC-richtlijnen (Konstantinides, 2020). Risicostratificatie van patiënten met acute longembolie wordt aanbevolen voor het bepalen van de therapeutische aanpak. De implicaties van deze risicoscore voor de patiëntenzorg in de acute setting op sommige domeinen zijn echter niet altijd duidelijk vanwege lacunes in het bewijs. Ook de ernst van de symptomen op het moment van de klinische presentatie, de hoge vroege sterftecijfers en de onzekerheden over de langetermijnresultaten (waaronder de kwaliteit van leven, het post-longemboliesyndroom en chronische trombo-embolische pulmonale hypertensie) leiden tot variatie in de therapeutische behandeling en soms het gebruik van rescue reperfusietherapie.
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**X < 1000 per jaar** **□ < 5000** **□ 5000-40.000** **□ > 40.000**

3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	□ **Ja**: hoe verhoudt deze aanbeveling zich tot de andere aanbevelingen uit deze module/ richtlijn of uit andere richtlijnen(modules)? Dient hier rekening mee gehouden te worden bij de implementatie of kan dit worden gezien als een losstaande aanbeveling? **Toelichting:** [toelichting] **X Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	Er is een sterke lobby voor het inzetten van percutane kathetergeleide interventie vanuit de farmaceutische industrie.	Adviezen van deze module zijn in lijn met de huidige ESC-richtlijn t.a.v. de behandeling van patienten met een acute intermediair-hoog risico longembolie.
b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	Onvoldoende kennis bij de zorgverleners over de aanbevelingen. Ook kan de sterke lobby vanuit de industrie t.a.v. de inzet van percutane kathetergeleide interventies van invloed zijn.	Adviezen van deze module zijn in lijn met andere nationale en internationale richtlijnen.
c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	-	-

d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	Verschillende meningen/inzichten tussen medische disciplines waaronder Longgeneeskunde/Interne Geneeskunde/Cardiologie/IC en Interventieradiologie	-
e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	-	Het geven van (orale) anticoagulantia vraagt geen andere organisatie van de huidige processen in de ziekenhuizen, zoals meer capaciteit etc.
f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	Er is een sterke lobby voor het inzetten van percutane kathetergeleide interventie vanuit de industrie; hier spelen mogelijk financiële belangen.	De kosten van (orale) anticoagulantia zijn veel lager die die van percutane kathetergeleide interventies

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	□ Patiënt/ cliënt (naaste) **X** Professional **X** Beroepsvereniging □ Ziekenhuis(bestuurder) □ Zorgverzekeraars/ NZa □ Zorginstituut [duiding nodig] □ …… *(graag aanvullen met alle relevante partijen, e.g., industrie)*
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	Aanbevelingen verwerken in lokale ziekenhuisprotocollen en deze implementeren in de klinische praktijk.
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X** < 1 jaar □ < 2 jaar

	□ < 3 jaar *[toelichting]*
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	□ **Ja* X Nee** **Toelichting:** [toelichting]

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

Evidence tables

Research question: What are the desirable and undesirable effects of percutaneous catheter-directed thrombolysis, systemic thrombolysis, or anticoagulation in patients with acute intermediate-high risk pulmonary embolism?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
RCT							
Kroupa, 2022	Type of study: RCT Setting and country: Tertiary care	Inclusion criteria: • Age > 18 years • CTCA conformed PE and symptom onset < 14 days prior	CDT + AC	Anticoagulation	Length of follow-up: 30 days Loss-to-follow-up: None	1. Mortality No death occurred at 30 days 2. Hemodynamic detoriation	

	center, Czech Republic Funding and conflicts of interest: Non-commercial	• Intermediate-high risk PE <u>Exclusion criteria</u>: • Active clinically significant bleeding • Any haemorrhagic stroke or a recent (< 6 months) ischaemic stroke/transient ischaemic attack • Recent < 3 months) cranial trauma or another active intracranial/ intraspinal process. • Major surgery within 7 days prior. • RV/LV ratio <0.7 • Active malignancy or other severe illness with expected survival < 2 years. • Haemoglobin level < 80 g/l; INR > 2.0, platelet count ≤100x$10^{9;}$ creatinine >200 μmol/l • Pregnant or breastfeeding, fertility without previous exclusion or gravidity • Allergic to thrombolytics or heparin or LMWH, contrast allergy, history of heparin-induced thrombocytopaenia			<u>Incomplete outcome data</u>: None	No instability in any patient observed 3. Bleeding complications Major bleeding No major bleeding episodes at 3 months. 4. Minor bleeding I: 1 (24%) C: 2 (3%) RR 0.46 (95%CI 0.05 to 4.38) 5. Recurrence of pulmonary embolism Not reported 6. Quality of life/PROMS Not reported 7. Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension Not reported	

		• Participation in another trial N total at baseline: Intervention: 12 Control: 11 Important prognostic factors[2]: age ± SD: I: 60 (14) C: 63 (15) Sex: I: 67% M C: 46% M					
Sadeghipour, 2022	Type of study: RCT Setting and country: Hospital, Iran Funding and conflicts of interest: Non-commercial	Inclusion criteria: • Adult patients (≥18 years) • presenting within 14 days from symptom onset with acute intermediate-high–risk PE Exclusion criteria: • Creatinine clearance less than 30 mL/min • Contraindications to fibrinolytic therapy (• Concomitant right heart thrombosis • Terminal illness. N total at baseline: Intervention: 48 (46 at FU) Control: 46 (39 at FU) Important prognostic factors[2] at FU:	CDT + AC A fixed dose of alteplase a rate of 0.5 mg per catheter per hour for 24 hours was administered. A fixed dose of unfractionated heparin (UFH; 500 units/hour) was administered to all the patients in the cCDT group during fibrinolytic therapy. After the termination of cCDT and removal of catheter(s), UFH was increased to therapeutic levels. Afterward, UFH was changed to twice-daily subcutaneous LMWH (enoxaparin, 1 mg/kg) in patients without procedural complication (eg, major vascular access	AC (LMWH, enoxaparin)	Length of follow-up: 3 months Loss-to-follow-up: Intervention: N 2 (4%) Reasons (2 did not accept on-site follow-up) Control: N 4 (9%) Reasons (4 did not accept on-site follow-up) Incomplete outcome data: Intervention: N 2 (4%) Reasons (2 did not accept on-site follow-up) Control: N 7 (15%) Reasons (4 did not accept on-site follow-up; 3 died before end of FU)	1. Mortality PE-related mortality I: 0 (0%) C: 2 (4%) All-cause mortality I: 0 (0%) C: 3 (7%) 2. Hemodynamic detoriation I: 0 (0%) C: 1 (2%) 3. Bleeding complications Major: I: 1 (2%) C: 0 (0%) Minor: I: 3 (6%) C: 0 (0%) 4. Recurrence of pulmonary embolism	

		Age ± SD: I: 57 (15) C: 57 (15) Sex: I: 72% M C: 72% M Prior PE: I: 1 (2%) C: 1 (2%)	complication or bleeding events) or unstable hemodynamics necessitating other invasive therapies. LMWH was planned to be continued for the first 48 hours after completion of fibrinolytic therapy.			Not reported 5. Quality of life/PROMS Not reported 6. Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension Not reported	
Zhang, 2018	Type of study: RCT Setting and country: Hospital, China Funding and conflicts of interest: No conflicts.	Inclusion criteria: Acute symptomatic PE confirmed by CTPA with an embolus located in at least 1 main or proximal lower lobe pulmonary artery and RV/LV ratio ≥0.9 obtained on echocardiographic examination Exclusion criteria: • age <18 or >80 years; • index PE symptom duration >14 days; • uncontrolled hypertension (SBP >180 mm Hg and/ or diastolic blood pressure (DBP) >110 mm Hg at presentation; • SBP <90 mm Hg for more than 15 min at presentation,	rt-PA at a dose of 30 mg over 2 hours with concomitant low molecular-weight heparin (LMWH)	LMWH anticoagulation alone	Length of follow-up: 3 months after discharge Loss-to-follow-up: None Incomplete outcome data: None	1. Mortality No death occurred at 3 months. 2. Hemodynamic detoriation Defined by the need for cardiopulmonary resuscitation, a drop in SBP by ≥40 mm Hg for ≥15 min or SBP <90 mm Hg for ≥15 min in accompanied with hypoperfusion of end-organ, or the need for vasopressors. I: 0 (0) C: 3 (9%) 3. Bleeding complications Major bleeding No major bleeding episodes at 3 months. Minor bleeding I: 8 (24%)	

		with or without signs of cardiogenic shock; • known significant bleeding risk; • active bleeding; known coagulation disorder; • gastrointestinal bleeding within the preceding 3 months; • history of any intracranial or intraspinal surgery or trauma or intracranial/ intraspinal bleeding; • arteriovenous malformation, or aneurysm; • major surgery, cataract surgery, trauma, obstetric delivery, cardiopulmonary resuscitation, or other invasive procedure <10 days; • pregnancy, lactation, or parturition <30 days; • participation in any other investigational drug or device study; • life expectancy <3 months; and				C: 1 (3%) RR 8.00 (95%CI 1.06 to 60.43) 4. Recurrence of pulmonary embolism I: 1 (3%) C: 2 (6%) RR 0.50 (95%CI 0.05 to 5.25) 5. Quality of life/PROMS Not reported 6. Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension Not reported	

		• inability to comply with study assessments. N total at baseline: Intervention: 33 Control: 33 Important prognostic factors[2]: age ± SD: I: 60 (13) C: 58 (11) Sex: I: 55% M C: 42% M Prior VTE I: 12% C: 9% Concomitant DVT I: 57% C: 48%					
Kucher, 2014	Type of study: RCT Setting and country: Hospital, Germany & Switzerland Funding and conflicts of interest: Commercial funding	Inclusion criteria: Symptomatic PE confirmed by contrast-enhanced computed tomography (CT) with embolus located in at least 1 main or proximal lower lobe pulmonary artery and RV to left ventricular dimension (RV/LV) ratio ≥1 obtained from the echocardiographic apical 4-chamber view. Exclusion criteria:	Unfractionated heparin (UFH) and an ultrasound-assisted catheter-directed thrombolysis (USAT) regimen of 10 mg recombinant tissue plasminogen activator (rtPA) over 15 hours per treated lung via the EkoSonic Endovascular System.	UFH alone	Length of follow-up: 90 days Loss-to-follow-up: None Incomplete outcome data: None	1. Mortality PE-related mortality No deaths after 3 months All-cause mortality I: 0 (0%) C: 1 (3%) 2. Hemodynamic detoriation No hemodynamic decompensation after 3 months 3. Bleeding complications Major bleeding	

		age <18 or >80 years; index PE symptom duration >14 days; insufficient echocardiographic image quality in the apical 4-chamber view that prohibited the measurement of the RV/LV ratio; known significant bleeding risk; administration of thrombolytic agents within the previous 4 days; active bleeding; known bleeding diathesis; known coagulation disorder; platelet count <100000/mm3; previous use of vitamin K antagonists with international normalized ratio >2.5 on admission; history of any intracranial or intraspinal surgery or trauma or intracranial/intraspinal bleeding; intracranial neoplasm, arteriovenous malformation, or aneurysm; gastrointestinal bleeding <3 months; internal eye surgery or hemorrhagic retinopathy <3 months; major surgery, cataract surgery, trauma, obstetric delivery,				No major bleeding episodes at 3 months. 4. Minor bleeding I: 3 (10%) C: 1 (3%) RR 2.90 (95%CI 0.32 to 26.30) 5. Recurrence of pulmonary embolism No recurrences after 3 months 6. Quality of life/PROMS Not reported 7. Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension Not reported	

		cardiopulmonary resuscitation, or other invasive procedure <10 days; allergy, hypersensitivity, or thrombocytopenia from heparin or rtPA; severe contrast allergy to iodinated contrast; known right-to-left cardiac shunt (eg, from a large patent foramen ovale or atrial septal defect); large (>10 mm) right atrial or RV thrombus; hemodynamic decompensation, defined as the need for cardiopulmonary resuscitation, or systolic blood pressure <90 mmHg for at least 15 minutes, or drop of systolic blood pressure by at least 40 mmHg for at least 15 minutes with signs of end-organ hypoperfusion (cold extremities or low urinary output <30 mL/h or mental confusion), or need for catecholamine administration to maintain adequate organ perfusion and a systolic blood pressure of >90 mmHg; severe hypertension on repeated readings (systolic >180 mmHg or					

		diastolic >105 mmHg); pregnancy, lactation, or parturition <30 days; participation in any other investigational drug or device study; life expectancy <90 days; and inability to comply with study assessments. N total at baseline: Intervention: 30 Control: 29 Important prognostic factors[2]: age ± SD: I: 64 (15) C: 62 (13) Sex: I: 63% F C: 41% F Prior PE I: 13% C: 7%					
Meyer, 2014	Type of study: RCT Setting and country: Hospital, Frnace, Germany, Poland, and Italy. Funding and conflicts of	Inclusion criteria: Age of 18 years or older, objectively confirmed acute pulmonary embolism with an onset of symptoms 15 days or less before randomization, right ventricular dysfunction confirmed by echocardiography or spiral computed	a single weight-based intravenous bolus (given over a period of 5 to 10 seconds) of the fibrinolytic agent tenecteplase. the administration of unfractionated heparin was started as an intravenous bolus immediately after	Patients assigned to placebo were given a single intravenous bolus of the same volume and appearance as the bolus of Tenecteplase the administration of unfractionated heparin was started as an intravenous bolus immediately after	Length of follow-up: 30 days Loss-to-follow-up: None Incomplete outcome data: None	1. Mortality PE-related mortality Not reported All-cause mortality I: 6 (1%) C: 9 (2%) OR 0.65 (95%CI 0.23 to 1.85) 2. Hemodynamic detoriation I: 8 (2%)	

	interest: Mixed (non-commercial and commercial)	tomography (CT) of the chest, and myocardial injury confirmed by a positive test for troponin I or troponin T. Exclusion criteria: See supplementary table of paper N total at baseline: Intervention: 506 Control: 499 Important prognostic factors[2]: Age ± SD: I: 66 (15) C: 65 (16) Sex: I: 48% M C: 46% M	randomization in both groups	randomization in both groups		C: 25 (5%) OR 0.30 (95%CI 0.14 to 0.68) 3. Bleeding complications Major bleedings I: 59 (12%) C: 12 (2.4%) RR 4.77 (95%CI 2.59 to 8.77) Minor bleedings I: 165 (33) C: 43 (9) RR 3.78 (95%CI 2.77 tot 5.17) 4. Recurrence of pulmonary embolism I: 1 (0%) C: 5 (1%) OR 0.20 (95%CI 0.02 to 1.68) 5. Quality of life/PROMS Not reported 6. Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension Not reported	
Sharifi, 2012	Type of study: RCT	Inclusion criteria: Adult patients presenting with signs and symptoms	ST (with tPA) + AC The dose of tPA was ≤50% of the standard	AC Warfarin was started at admission in all patients.	Length of follow-up: Mean 28 ± 5 months Loss-to-follow-up:	1. Mortality PE-related mortality Not reported	

	Setting and country: USA Funding and conflicts of interest: Not reported	suggestive of PE plus imaging documentation on computed tomographic angiography or ventilation/perfusion scanning were potentially eligible for the study. "Moderate" PE was defined as the presence of signs and symptoms of PE plus computed tomographic pulmonary angiographic involvement of >70% involvement of thrombus in ≥2 lobar or left or right main pulmonary arteries (Figure 1) or by a high probability ventilation/perfusion scan showing ventilation/perfusion mismatch in ≥2 lobes <u>Exclusion criteria</u>: Onset of symptoms >10 days; >8 hours since the start of parenteral anticoagulation; systemic arterial systolic blood pressure <95 or ≥200/100 mm Hg; eligibility for full-dose thrombolysis; a contraindication to unfractionated or low-molecular-weight heparin; severe	dose (100 mg) commonly used for the treatment of PE, which we termed "safe dose" thrombolysis. Warfarin was started at admission in all patients. All patients received either unfractionated heparin or subcutaneous enoxaparin, with initial preference given to the latter drug.	All patients received either unfractionated heparin or subcutaneous enoxaparin, with initial preference given to the latter drug.	Intervention: N 3 (5%) Reasons (Not stated) Control: N 4 (7%) Reasons (Not stated) <u>Incomplete outcome data</u>: Intervention: N 3 (5%) Reasons (Not stated) Control: N 4 (7%) Reasons (Not stated)	All-cause mortality I: 1 (2%) C: 3 (5%) RR 0.33 (95%CI 0.04 to 3.06) 2. Hemodynamic detoriation Not reported 3. Bleeding complications No bleeding event 4. Recurrence of pulmonary embolism I: 0 (0%) C: 3 (5%) 5. Quality of life/PROMS Not reported 6. Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension Not reported	

		thrombocytopenia (platelet count <50,000/mm3); major bleeding within <2 months requiring transfusion; surgery or major trauma within <2 weeks; brain mass; neurologic surgery, intracerebral hemorrhage, or subdural hematoma within <1 year; end-stage illness with no plan for PE treatment; and an inability to perform echocardiography. <u>N total at baseline</u>: Intervention: 61 Control: 60 <u>Important prognostic factors[2]</u>: Age ± SD: I: 58 (9) C: 59 (10) Sex: I: 46% M C: 45% M Prior VTE I: 13 (21%) C: 12 (20%) Concomitant DVT I: 35 (57%) C: 33 (55%)					

Fasullo, 2011	Type of study: RCT Setting and country: Emergency department, Italy Funding and conflicts of interest: Not stated	Inclusion criteria: (1) symptoms onset since no more than 6 hours, for first episode of acute SPE; (2) normal blood pressure [systolic blood pressure (SBP) 100 mm Hg]; (3) RVD at echocardiogram; (4) positive lung spiral computed tomography (CT) and (5) dyspnea, chest pain, tachypnea, hypoxemia PO2 75 mm Hg, PCO2 40 mm Hg, oxygen saturation 90% in room air, D-dimer elevation, electrocardiography (ECG) with S1-Q3-T3 pattern, inversion of T waves in V1 to V4, a right bundle-branch block or right axis deviation. Exclusion criteria: active internal bleeding, recent intracranial bleeding, intracranial tumor or seizure history, ischemic stroke until 2 months, neurosurgery during last month, recent surgery within 10 days, puncture of uncompressible vessel within 10 days, trauma within 15 days, uncontrolled	ST (100 mg of alteplase (Actilyse as a 10-mg bolus, followed by a 90-mg intravenous infusion over a period of 2 hours) In addition to alteplase, both groups continued to receive unfractionated heparin treatment (1000 U/hr and/or accordingly activated partial thromboplastin time [aPTT]), in combination with warfarin (started on day 1 after randomization), until the international normalized ratio was within the therapeutic range for 2 consecutive days; after this point, heparin was stopped, and only warfarin was kept after discharge and during follow-up	AC Matching placebo to alteplase. In addition to placebo, both groups continued to receive unfractionated heparin treatment (1000 U/hr and/or accordingly activated partial thromboplastin time [aPTT]), in combination with warfarin (started on day 1 after randomization), until the international normalized ratio was within the therapeutic range for 2 consecutive days; after this point, heparin was stopped, and only warfarin was kept after discharge and during follow-up	Length of follow-up: 6 months Loss-to-follow-up: None Incomplete outcome data: None	1. Mortality PE-related mortality I: 0 C: 4 (11%) All-cause mortality I: 0 C: 6 (17%) 2. Hemodynamic detoriation Not reported 3. Bleeding complications Major bleeding I: 2 (5%) C: 1 (3%) RR 1.89 (95%CI 0.18 to 19.95) Minor bleeding I: 16 (43%) C: 8 (22%) RR 1.89 (95%CI 0.93 to 3.86) 4. Recurrence of pulmonary embolism I: 0 C: 5 5. Quality of life/PROMS Not reported 6. Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without	

		hypertension (SBP ≥180 mm Hg and diastolic BP ≥110 mm Hg), hemorrhagic disorder of thrombocytopenia (100,000), severe impaired hepatic or renal function, gastrointestinal bleeding within 10 days, pregnancy, age older than 75 years. Patients were also excluded if they had arterial aneurysm or arterial/venous malformation and cancer at increased risk for bleeding. In addition, patients with chronic pulmonary hypertension, severe chronic obstructive pulmonary disease and who had received therapeutic doses of heparin (unfractionated or low-molecular-weight heparin) for more than 72 hours before randomization, thrombolytic treatment within the previous 4 days, or glycoprotein IIb/IIIa antagonists within the preceding 7 days were also excluded, and so were excluded the ones who				pulmonary hypertension Not reported	

		were under oral anticoagulation <u>N total at baseline</u>: Intervention: 37 Control:3 35 <u>Important prognostic factors</u>[2]: For example age ± SD: I: 55 (17) C: 57 (16) Sex: I: 57% M C: 57% M					
Konstantinides, 2002	Type of study: RCT Setting and country: Germany Funding and conflicts of interest: Commercial	<u>Inclusion criteria</u>: echocardiographically detected right ventricular dysfunction, defined as right ventricular enlargement combined with loss of inspiratory collapse of the inferior vena cava, without left ventricular or mitral-valve disease12; echocardiographically detected pulmonary-artery hypertension,13 defined as a tricuspid regurgitant jet velocity greater than 2.8 m per second, followed by confirmation of pulmonary embolism (by ventilation–perfusion lung scanning, spiral	Heparin plus alteplase intravenous bolus of 5000 U of unfractionated heparin before undergoing further diagnostic workup. Patients who met the inclusion criteria and were enrolled in the study were then randomly assigned to receive 100 mg of alteplase as a 10-mg bolus, followed by a 90-mg intravenous infusion over a period of two hours, or matching placebo. In addition to alteplase or placebo, patients in both groups received an	Heparin plus placebo	<u>Length of follow-up</u>: Based on figure 1, 30 days <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	1. Mortality PE-related mortality Not reported All-cause mortality I: 4 (3%) C: 3 (2%) RR 1.56 (95%CI 0.36 to 6.83) 2. Hemodynamic detoriation Not reported 3. Bleeding complications Major bleeding I: 1 (5%) C: 5 (3%) RR 0.23 (95%CI 0.03 to 1.97) Minor bleeding Not reported	

		computed tomography [CT], or pulmonary angiography); a diagnosis of precapillary pulmonary hypertension based on catheterization of the right side of the heart, defined as a mean pulmonary-artery pressure above 20 mm Hg and a pulmonary-capillary wedge pressure below 18 mm Hg, followed by confirmation of pulmonary embolism; or new electrocardiographic signs of right ventricular strain (defined as complete or incomplete right bundlebranch block, S waves in lead I combined with Q waves in lead III, or inverted T waves in precordial leads V1, V2, and V3), followed by confirmation of pulmonary embolism. <u>Exclusion criteria</u>: age over 80 years; hemodynamic instability, defined as persistent arterial hypotension (i.e., systolic	intravenous infusion of unfractionated heparin.			4. Recurrence of pulmonary embolism I: 4 C: 4 RR 1.17 (95%CI 0.30 to 4.57) 5. Quality of life/PROMS Not reported 6. Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension Not reported	

		pressure below 90 mm Hg), with or without signs of cardiogenic shock; onset of symptoms more than 96 hours before diagnosis; thrombolytic treatment, major surgery, or biopsy within the preceding 7 days; major trauma within the preceding 10 days; stroke, transient ischemic attack, craniocerebral trauma, or neurologic surgery within the preceding 6 months; gastrointestinal bleeding within the preceding 3 months; uncontrolled hypertension; a known bleeding disorder; known inability to tolerate alteplase; known diabetic retinopathy; current therapy with an oral anticoagulant; current pregnancy or lactation; a life expectancy of less than 6 months because of underlying disease; or planned use of thrombolytic agents for extensive deep-vein thrombosis. <u>N total at baseline</u>:					

		Intervention: 118 Control: 138 Important prognostic factors[2]: age ± SD: I: C: Sex: I: 46% M C: 49% M					
Cohort studies							
Krishnan, 2022	Type of study: Cohort study Setting and country: Nationwide Inpatient Sample from 2017, USA Funding and conflicts of interest: None	Inclusion criteria: Patients above the age of 18 years admitted with the principal diagnosis of Acute PE with cor pulmonale in 2017 Exclusion criteria: None N total at baseline: Intervention1: 2460 Intervention2: 1340 Control: 9525 Important prognostic factors[2]: Mean age: I1: 61 I2: 61 C: 65 Sex: I1: 51% M I2: 59% M C: 48% M	Intervention1: CDT Intervention2: ST	AC	Length of follow-up: Not reported Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	1. Mortality PE-related mortality Not reported All-cause mortality CDT vs AC OR 0.61 (95%CI 0.33 to 1.11) CDT vs ST OR 0.33 (95%CI 0.14 to 0.61) 2. Hemodynamic detoriation Not reported 3. Bleeding complications Not reported 4. Recurrence of pulmonary embolism Not reported 5. Quality of life/PROMS Not reported	Analyses adjusted for age, liver disease, obesity, OSA, hypertension, race, annual income, Charlson Comorbidity Score, and hospital bed size.

						6. Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension Not reported	
Hobohm, 2021	Type of study: Cohort study Setting and country: Database of the federal Office of Statistics, Germany Funding and conflicts of interest: Non-commercial	Inclusion criteria: Hospitalized patients diagnosed with PE between the years 2005 and 2016 Exclusion criteria: patients who underwent (i) surgical embolectomy or (ii) percutaneous treatment (thrombus fragmentation; or rotational thrombectomy) without thrombolytic drugs at any dosage were excluded from all analyses. Patients who received both systemic thrombolysis and CDT were also excluded from analysis. N total at baseline: Intervention: 1175 Control: 40728 Important prognostic factors[2]: Age median (IQR):	CDT	ST Or no ST (AC alone)	Length of follow-up: Not reported Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	1. Mortality PE-related mortality Not reported All-cause mortality CDT vs AC OR 0.45 (95%CI 0.33 to 0.62) CDT vs ST (among hemodynamically stable PE patients) OR 0.55 (95%CI 0.40 to 0.75) 2. Hemodynamic detoriation Not reported 3. Bleeding complications Not reported 4. Recurrence of pulmonary embolism Not reported 5. Quality of life/PROMS Not reported 6. Chronic thrombo-embolic pulmonary	We fitted multivariate logistic regression models including the following covariates chosen based on clinical relevance and no obvious collinearity: age, sex, cancer (ICD codes C00-C97), coronary artery disease (ICD code I25), heart failure (ICD code I50), chronic obstructive pulmonary disease (COPD, ICD code J44), essential arterial hypertension (ICD code I10), diabetes mellitus (ICD codes E10–E14), chronic renal insufficiency (chronic renal insufficiency stages 3–5 with glomerular filtration rate <60mL/min/1.73 m2: ICD codes N18.3, N18.83, N18.84, N18.4, N18.5), surgery during inhospital stay (OPS code 5), tachycardia (ICD codes I47 and R000), syncope (ICD code R55), and hypoxia (ICD code J96). The multivariate analyses were

		I: 68 (53-76) C: 69 (57-77) Sex: I: 49% M C: 48% M				hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension Not reported	extended by adding the Charlson index.
Lin, 2021	Type of study: Cohort study Setting and country: Health insurance database, Taiwan Funding and conflicts of interest: Non-commercial	Inclusion criteria: Patients who were first admitted for PE (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], code 415.1) between January 1, 2001, and December 31, 2013, were identified. Exclusion criteria: (1) had missing demographical data (<0.1%), (2) were aged <20 years, or (3) were not treated by thrombolysis during the index PE admission. N total at baseline: Intervention: 145 Control: 1158 Important prognostic factors[2]: Age ± SD: I: 61 (16) C: 62 (16)	CDT (thrombolytic agent received through multi-side-hole catheters) Thrombolytic agent consisted of: • tPA • Uorkinase • Streptokinase	ST (thrombolytic agent NOT received through multi-side-hole catheters)	Length of follow-up: Mean follow-up of 3.8 yrs and 3.4 yrs for CDT and ST, respectively Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Only results of the IPTW analyses are reported. Adjusted for sex, hyperlipidemia, hyperthyroidism, previous stroke, Charlson Comorbidity Index score, statin use, anticoagulant use, and intubation. 1. Mortality PE-related mortality Not reported All-cause mortality I: 22 (15%) C: 250 (22%) OR 0.49 (95%CI 0.36 to 0.67) 2. Hemodynamic detoriation Not reported 3. Bleeding complications Major bleeding I: 13 (9%) C: 91 (8%) OR 1.02 (95%CI 0.75 to 1.37) Minor bleeding	

		Sex: I: 39% M C: 46% M History of PE I: 2 (1%) C: 13 (1%)				Not reported 4. Recurrence of pulmonary embolism Among the group who survived initial hospitalization I: 22 (18% out of 123) C: 219 (24% out of 908) HR 0.84 (95%CI 0.72 to 0.98) 5. Quality of life/PROMS Not reported 6. Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension Not reported	
Stein, 2020	Type of study: Cohort study Setting and country: Nationwide Inpatient sample, USA Funding and conflicts of interest: None	<u>Inclusion criteria</u>: Stable patients with acute PE and acute cor pulmonale. Stable patients were defined as not in shock and not on ventilator support. <u>Exclusion criteria</u>: Patients who underwent pulmonary embolectomy or received intravenous thrombolytic therapy. <u>N total at baseline</u>:	CDT plus AC	AC	<u>Length of follow-up</u>: Not reported <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	1. Mortality PE-related mortality Not reported All-cause mortality I: 30 (4%) C: 395 (7%) OR 0.56 (95%CI 0.38 to 0.82) 2. Hemodynamic detoriation Not reported 3. Bleeding complications	Patients with PE an acute pulmonale were assumed to treated with anticoagulants if they did not receive intravenous thrombolytic therapy, catheter-directed thrombolytic therapy, or pulmonary embolectomy. Authors also assumed that patients treated with catheter-directed thrombolysis also received anticoagulants.

		Intervention: 735 Control: 5605 <u>Important prognostic factors[2]</u>: Age ± SD: I: 60 (13) C: 60 (11) Sex: I: 47% M C: 45% M				Not reported 4. Recurrence of pulmonary embolism Not reported 5. Quality of life/PROMS Not reported 6. Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension Not reported	Patients were matched on age, gender, and co-morbid conditions.
Arora, 2017	Type of study: Cohort study Setting and country: National Readmission Database, USA Funding and conflicts of interest: None	<u>Inclusion criteria</u>: Patient admitted for PE and received trombolysis <u>Exclusion criteria</u>: we excluded patients with secondary diagnostic codes for acute ST elevation myocardial infarction, ischemic stroke, and hospice care. We excluded patients with age <18 years, with missing data for age, gender, or mortality. We also excluded procedures performed in the month of December, as we did	CDT	ST	<u>Length of follow-up</u>: Not reported <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	1. Mortality PE-related mortality Not reported All-cause mortality (absolute numbers not reported) I: 6% C: 15% OR 0.37 (95%CI 0.28 to 0.49) 2. Hemodynamic detoriation Not reported 3. Bleeding complications Not reported 4. Recurrence of pulmonary embolism	A propensity score, which was assigned to each principal hospitalization, was based on multivariable logistic regression model that examined the impact of 12 variables (patient demographics, co-morbidities, and hospital characteristics) on the likelihood of treatment assignment

		not have follow-up data for the same. N total at baseline: Intervention: 1128 Control: 2256 Important prognostic factors[2]: Sex: I: 53% M C: 52% M				Not reported 5. Quality of life/PROMS Not reported 6. Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension Not reported	
Patel, 2015	Type of study: Cohort study Setting and country: Nationwide Inpatient Sample, USA Funding and conflicts of interest: Not reported	Inclusion criteria: Patients admitted with principal diagnosis of PE who received thrombolysis. Exclusion criteria: We excluded all observations with <18 years of age. We further excluded patients with secondary diagnostic codes for deep vein thrombosis, acute ST elevation myocardial infarction, and ischemic stroke. N total at baseline: Intervention: 352 (unmatched) Control: 1169 (unmatched) Important prognostic factors[2]: Age ± SD:	CDT	ST	Length of follow-up: Not reported Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	1. Mortality PE-related mortality All-cause mortality I: 13% C: 22% OR 0.55 (95%CI 0.36 to 0.85) 2. Hemodynamic detoriation Not reported 3. Bleeding complications Not reported 4. Recurrence of pulmonary embolism Not reported 5. Quality of life/PROMS Not reported 6. Chronic thrombo-embolic pulmonary hypertension (CTEPH)/Chronic	To adjust the possible confounding variables and to ameliorate the effect of selection and indication bias, propensity score matching was done after generating the propensity scores from demographic covariates including the Deyo-modification of Charlson score, cardiopulmonary arrest, saddle PE, and shock.

		I: 59 (15) C: 58 (16) Sex: I: 48% M C: 42% M				thrombo-embolic pulmonary disease (CTEPD) without pulmonary hypertension Not reported	

Risk of bias assessment RCT

5 **Research question:** What are the desirable and undesirable effects of percutaneous catheter-directed thrombolysis, systemic thrombolysis, or anticoagulation in patients with acute intermediate-high risk pulmonary embolism?

Study reference	**Was the allocation sequence adequately generated?**	**Was the allocation adequately concealed?**	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?**	**Was loss to follow-up (missing outcome data) infrequent?**	**Are reports of the study free of selective outcome reporting?**	**Was the study apparently free of other problems that could put it at a risk of bias?**	**Overall risk of bias** **If applicable/necessary, per outcome measure**
Kroupa, 2022	Probably no Reason: Authors stated: “randomized	Probably no Reason: Authors stated: “randomized	Probably no Reason: Nothing stated on blinding.	Definitely yes.	Probably yes Reason: Outcomes mentioned in Methods	Definitely yes Reason: No other problems	High risk of bias Reason: No information on the

	using a simple evelope method [..] in a 1:1 ratio."	using a simple evelope method [..] in a 1:1 ratio."		Reason: No participants were lost during the study.	section were reported in the results section.		randomization, allocation concealment or blinding of participants.
Sadeghipour, 2022	Probably yes Reason: Authors stated: "Randomization was carried out in a 1:1 ratio to cCDT plus anticoagulation vs anticoagulation monotherapy via an electronic web-based system with permuted blocks of 4 and concealed allocation sequences."	Probably yes Reason: Authors stated: "Randomization was carried out in a 1:1 ratio to cCDT plus anticoagulation vs anticoagulation monotherapy via an electronic web-based system with permuted blocks of 4 and concealed allocation sequences."	Probably no Reason: Data collectors and outcome assessors were blinded. Rest of team were not blinded as no placebo or sham was used.	Probably yes Reason: Although more patients did not accept follow-up in the control group than intervention group, numbers are low.	Definitely yes Reason: Trial was registered and stated outcomes were mentioned in the results section.	Definitely yes Reason: No other problems	Low risk of bias Reason: For the outcome of interest and reported, the not blinding of patients or participants will most likely not affect the estimate.
Zhang, 2018	Probably no Reason: Only stated the following: "[..] randomly assigned by envelopes to receive [..]".	Probably no Reason: Only stated the following: "[..] randomly assigned by envelopes to receive [..]".	Probably no Reason: Nothing stated on blinding.	Definitely yes. Reason: No participants were lost during the study.	Probably yes Reason: Outcomes mentioned in Methods section were reported in the results section. However, clinical trial registry for this trial could be found.	Definitely yes Reason: No other problems	High risk of bias Reason: No information on the randomization, allocation concealment or blinding of participants.
Kucher, 2013	Probably no Reason: Authors stated: "Randomization was performed in blocks of 4 without stratification."	Probably no Reason: Authors stated: "Randomization was performed in blocks of 4 without stratification."	Probably no Reason: Nothing stated on blinding.	Definitely yes. Reason: No participants were lost during the study.	Definitely yes Reason: Trial was registered before first results and outcomes were reported in the paper.	Definitely yes Reason: First author was a consultant for the sponsor (device company) and the results are in favor of the sponsor.	High risk of bias Reason: No information on the randomization, allocation concealment or blinding of participants. Trial was sponsored by a device company for which the first author is a consultant.
Meyer, 2014	Probably yes	Probably yes	Probably yes	Definitely yes.	Probably yes	Probably yes	Low risk of bias

	Reason: Authors stated: “Eligible patients underwent central randomization with the use of a computerized Internetbased system. Randomization was stratified by center and, within centers, was performed in blocks to ensure balanced distribution of the treatment groups.	Reason: Placebo similar to intervention was used.	Reason: Placebo similar to intervention was used. Data was concealed from the investigators.	Reason: No participants were lost during the study.	Reason: Outcomes mentioned in Methods section were reported in the results section. However, clinical trial registry for this trial could not be found.	Reason: Trial received mixed sponsor ship. However, authors stated: “None of the trial funders had any role in the design or conduct of the trial, the analysis of the data, or the preparation of the manuscript.”	Reason: No issues
Sharifi, 2012	Probably yes Reason: Authors only stated: “After evaluation of the patient, the study investigator placed a telephone call to the study center, and, by opening of sealed envelopes, randomization to the TG or CG was made.”	Probably yes Reason: Authors only stated: “After evaluation of the patient, the study investigator placed a telephone call to the study center, and, by opening of sealed envelopes, randomization to the TG or CG was made.”	Probably no Reason: Nothing stated on blinding.	Probably yes Reason: Number of participants lost was low, even though no reasons were provided.	Probably yes Reason: Outcomes mentioned in Methods section were reported in the results section. However, clinical trial registry for this trial could not be found.	Probably yes Reason: Funding of the trial is unclear.	Low risk of bias Reason: No issues
Fasullo, 2011	Probably yes Reason: Authors stated: “Randomization was performed by using a preliminary computer algorithm, [..].”	Probably yes Reason: Authors stated: “[..], and the assignment of all patients was decided at admission, before echocardiogram and before lung spiral lung CT by an external team of physicians (at least 2) who were blinded about study protocol.”	Probably yes Reason: Authors only stated: “Two blinded physicians evaluated the clinical status and if recurrence of PE was present and side effects warfarin treatment (bleedings) were also recorded.” Participants did receive a placebo to alteplase.	Definitely yes. Reason: No participants were lost during the study.	Probably yes Reason: Outcomes mentioned in Methods section were reported in the results section.	Probably yes Reason: Funding of the trial is unclear.	Low risk of bias Reason: No issues
Konstantinides, 2002	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably no	Some concerns

	Reason: Authors stated: "Randomization was performed on a 1:1 basis with a fixed block size of six patients at each center, according to a standard randomization program.	Reason: Nothing stated on allocation concealment	Reason: Placebo was used, and data was analyzed by an independent organization.	Reason: Not specifically stated, but most likely no participants were lost.	Reason: Outcomes mentioned in Methods section were reported in the results section.	Reason: Author was employed by sponsor and effect estimate is in favor of the sponsor.	Reason: Influence of sponsor cannot be ruled out.

Risk of bias assessment Cohort studies

Research question: What are the desirable and undesirable effects of percutaneous catheter-directed thrombolysis, systemic thrombolysis, or anticoagulation in patients with acute intermediate-high risk pulmonary embolism?

Author, year	Selection of participants Was selection of exposed and non-exposed cohorts drawn from the same population?	Exposure Can we be confident in the assessment of exposure?	Outcome of interest Can we be confident that the outcome of interest was not present at start of study?	Confounding-assessment Can we be confident in the assessment of confounding factors?	Confounding-analysis Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables?	Assessment of outcome Can we be confident in the assessment of outcome?	Follow up Was the follow up of cohorts adequate? In particular, was outcome data complete or imputed?	Co-interventions Were co-interventions similar between groups?	Overall Risk of bias
Krishnan, 2022	Definitely yes Reason: All participants came from the same database.	**Probably no** Reason: ICD-10 codes were used. However, no checks were performed if the ICD code matched the intervention.	Unclear Reason: It is unclear how the outcome was determined	**Definitely no** Reason: Selection of confounding factors was based on univariate analyses.	**Definitely no** Reason: Although standard multivariate analyse was used, confounding by indication is still an issue.	Unclear Reason: It is unclear how the outcome was determined	Unclear Reason: It is unclear what the duration of follow-up was	Unclear Reason: no information provided	**High (All outcomes)** **Confounding by indication is an issue**
Hobohm, 2021	Definitely yes Reason: All participants came from the same database.	**Probably no** Reason: ICD-10-GM codes were used. However, no checks were performed if the ICD code matched the intervention.	Unclear Reason: It is unclear how the outcome was determined	Definitely yes Reason: Appriopate factors used in adjustment	**Definitely no** Reason: Although standard multivariate analyse was used, confounding by indication is still an issue.	Definitely yes Reason: ICD-10-GM codes were used.	Unclear Reason: It is unclear what the duration of follow-up was	Unclear Reason: no information provided	**High (all outcomes)** **Confounding by indication is an issue**
Lin, 2021	Definitely yes Reason: All participants came from a health	**Probably no** Reason: Claims data was used for the exposure.	Probably yes Reason:	Definitely yes Reason: Appriopate	**Probably no** Reason: IPTW analyses used. Confounding by	Probably yes Reason: Mortality was defined as	Definitely yes Reason: Average follow-up was at least 3 years.	Probably yes Reason: Medication use was adjusted for.	**High (All outcomes)**

	insurance database.	However, no checks were performed if the claim matched the intervention	Mortality was defined as removal from the database. Major bleeding and recurrent PE were not clearly defined.	factors used in adjustment	indication may still be an issue	removal from the database. Major bleeding and recurrent PE were not clearly defined.			**Confounding by indication is an issue**
Stein, 2020	Definitely yes Reason: All participants came from Nationwide Inpatient sample.	Unclear Reason: It is unclear how exposure was determined.	Unclear Reason: It is unclear how the outcome was determined	Probably yes Reason: Patients were matched. However, only a limited number of factors were used.	**Definitely no** Reason: Although a matched analysis was used, confounding by indication is still an issue.	Unclear Reason: It is unclear how the outcome was determined	Unclear Reason: It is unclear what the duration of follow-up was	Unclear Reason: no information provided	**High (all outcomes)** **Too many items were unclear and confounding by indication is an issue**
Arora, 2017	Definitely yes Reason: All participants came from the National Readmission Database	**Probably no** Reason: ICD-9-CM codes were used. However, the interventions researched do not have unique coding.	Unclear Reason: It is unclear how the outcome was determined	Definitely yes Reason: Apprioprate factors used in adjustment	**Probably no** Reason: Propensity score matched analyses used. Confounding by indication may still be an issue	Unclear Reason: It is unclear how the outcome was determined	Unclear Reason: It is unclear what the duration of follow-up was	Probably yes Reason: Cohort characteristics were balanced after matching.	**High (All outcomes)** **Information on the outcome and follow-up would be helpful. Confounding by indication is an issue**
Patel, 2015	Definitely yes Reason: All participants came from Nationwide Inpatient sample.	**Probably no** Reason: ICD-9-CM codes were used. However, the interventions researched do not have unique coding.	Unclear Reason: It is unclear how the outcome was determined	Definitely yes Reason: Apprioprate factors used in adjustment	**Probably no** Reason: Propensity score matched analyses used. Confounding by indication may still be an issue	Unclear Reason: It is unclear how the outcome was determined	Unclear Reason: It is unclear what the duration of follow-up was	Unclear Reason: no information provided	**High (All outcomes)** **Information on the outcome and follow-up would be helpful. Confounding by indication is an issue**

Table of excluded studies from Planer (2023)

Reference	Reason for exclusion
Jerjes-Sanchez C, Ramírez-Rivera A, de Lourdes García M, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. J Thromb Thrombolysis 1995;2:227-9.	Published before 2000
Goldhaber SZ, Come PC, Lee RT, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993;341:507-11.	Published before 2000
Dalla-Volta S, Palla A, Santolicandro A, et al. PAIMS 2: Alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. Plasminogen activator Italian multicenter study 2. J Am Coll Cardiol 1992;20:520-6	Published before 2000
Tissue plasminogen activator for the treatment of acute pulmonary embolism: a collaborative study by the PIOPED Investigators. Chest 1990;97:528-33.	Published before 2000
Dotter CT, Seaman AJ, Rösch J, et al. Streptokinase and heparin in the treatment of pulmonary embolism: a randomized comparison. Vasc Endovascular Surg 1979;13:42-52	Published before 2000
Ly B, Arnesen H, Eie H, et al. A controlled clinical trial of streptokinase and heparin in the treatment of major pulmonary embolism. Acta Med Scand 1978;203:465-70.	Published before 2000
Tibbutt DA, Lee GDJ, Sharp AA, et al. Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonary embolism. BMJ 1974;1:343-7.	Published before 2000
Miller GAH, Sutton GC, Kerr IH, et al. Comparison of streptokinase and heparin in treatment of isolated acute massive pulmonary embolism. BMJ 1971;2:681-4.	Published before 2000
Urokinase Pulmonary Embolism Trial Study Group. Urokinase Pulmonary Embolism trial: Phase 1 results. JAMA 1970;214:2163-72.	Published before 2000
Geller BJ, Adusumalli S, Pugliese SC, et al. Outcomes of catheter-directed versus systemic thrombolysis for the treatment of pulmonary embolism: a realworld analysis of national administrative claims. Vasc Med 2020;25:334-40.	Despite using an advanced method for confounding, no effect estimates were reported.
Macovei L, Presura RM, Arsenescu Georgescu C. Systemic or local thrombolysis in high-risk pulmonary embolism. Cardiol J. 2015;22(4):467-74. doi: 10.5603/CJ.a2014.0103. Epub 2015 Jan 7. PMID: 25563712.	Wrong comparison
Beyer SE, Shanafelt C, Pinto DS, et al. Utilization and outcomes of thrombolytic therapy for acute pulmonary embolism: a nationwide cohort study. Chest 2020;157:645-53.	Only the analysis of CDT-US vs CDT was adjusted for confounding.
Liang NL, Avgerinos ED, Singh MJ, et al. Systemic thrombolysis increases hemorrhagic stroke risk without survival benefit compared with catheter-directed intervention for the treatment of acute pulmonary embolism. J Vasc Surg Venous Lymphat Disord 2017;5:171-176.e1	Overlap in sample from the same database used by other included studies.

Ahmed MA, Abdelsalam SI, Elmorsy RA. Value of thrombolytic therapy for submassive pulmonary embolism patients. Egypt J Chest Dis Tuberc 2018;67:413-8	Cohort study; included less than 500 patients
Bradley M, Bull T, Hountras P, et al. Pragmatic use of catheter-directed thrombolysis in venous thromboembolism and a comparative evaluation with traditional therapies in submassive pulmonary embolism. J Pharm Pract 2022;35:738-46.	Cohort study; included less than 500 patients
Gorgis S, Mawri S, Dabbagh MF, et al. Ultrasound-assisted catheter-directed thrombolysis versus anticoagulation alone for management of submassive pulmonary embolism. J Cardiol 2022;80:441-8.	Cohort study; included less than 500 patients
Zimmermann L, Laufs U, Petros S, et al. Outcome after thrombolysis in patients with intermediate high-risk pulmonary embolism: a propensity score analysis. J Emerg Med 2022;62:378-89.	Cohort study; included less than 500 patients
Harrison E, Kim JS, Lakhter V, et al. Safety and efficacy of catheter directed thrombolysis (CDT) in elderly with pulmonary embolism (PE). BMJ Open Respir Res 2021;8:6-10	Cohort study; included less than 500 patients
Kline TM, Rodino AM, Dorszynski A, et al. Ultrasound-assisted catheterdirected thrombolysis versus systemic anticoagulation alone for submassive pulmonary embolism. J Thromb Thrombolysis 2021;52:130-7	Cohort study; included less than 500 patients
Weng C, Wang X, Huang L, et al. Low-dose urokinase thrombolytic therapy for patients with acute intermediate-high-risk pulmonary embolism: a retrospective cohort study. PLoS One 2021;16:e0248603.	Cohort study; included less than 500 patients
Yilmaz ES, Uzun O. Low-dose thrombolysis for submassive pulmonary embolism. J Investig Med 2021;69:1439-46.	Cohort study; included less than 500 patients
D'Auria S, Sezer A, Thoma F, et al. Outcomes of catheter-directed thrombolysis vs. standard medical therapy in patients with acute submassive pulmonary embolism. Pulm Circ 2020;10:2045894019898368.	Cohort study; included less than 500 patients
Lee JK, Chen WH, Lin YS, Chang CH, Chen TH. Comparison of Effectiveness between Anticoagulation and Thrombolysis Therapy for Pulmonary Embolism in Patients Complicated with Shock: A Nationwide Population-Based Study. Thromb Haemost. 2020 Aug;120(8):1208-1216.	Cohort study which included only patients with shock, no intermediate-high risk patients were included
Rehman NU, Dar MI, Bansal M, et al. Clinical outcomes of submassive pulmonary embolism thrombolysis — an Indian experience. Egypt Heart J 2020;72:87	Cohort study; included less than 500 patients
Sharifi M, Awdisho A, Schroeder B, et al. Retrospective comparison of ultrasound facilitated catheter-directed thrombolysis and systemically administered half-dose thrombolysis in treatment of pulmonary embolism. Vasc Med 2019;24:103-9.	Cohort study; included less than 500 patients
Avgerinos ED, Abou Ali AN, Liang NL, et al. Catheter-directed interventions compared with systemic thrombolysis achieve improved ventricular function recovery at a potentially lower complication rate for acute pulmonary embolism. J Vasc Surg Venous Lymphat Disord 2018;6:425-32.	Cohort study; included less than 500 patients
Schissler AJ, Gylnn RJ, Sobieszczyk PS, et al. Ultrasound-assisted catheterdirected thrombolysis compared with anticoagulation alone for treatment of intermediate-risk pulmonary embolism. Pulm Circ 2018;8:2045894018800265.	Cohort study; included less than 500 patients
Sista AK, Friedman OA, Dou E, et al. A pulmonary embolism response team's initial 20-month experience treating 87 patients with submassive and massive pulmonary embolism. Vasc Med 2018;23:65-71.	Cohort study; included less than 500 patients
Klevanets J, Starodubtsev V, Ignatenko P, et al. Systemic thrombolytic therapy and catheter-directed fragmentation with local thrombolytic	Cohort study; included less than 500 patients

therapy in patients with pulmonary embolism. Ann Vasc Surg 2017;45:98-105.	
Avgerinos ED, Liang NL, El-Shazly OM, et al. Improved early right ventricular function recovery but increased complications with catheter-directed interventions compared with anticoagulation alone for submassive pulmonary embolism Presented in the Plenary Session at the 2015 Vascular Annual Meeting. J Vasc Surg Venous Lymphat Disord 2016;4:268-75.	Cohort study; included less than 500 patients
Yoo JW, Choi HC, Lee SJ, et al. American Journal of Emergency Medicine Comparison between systemic and catheter thrombolysis in patients with pulmonary embolism. Am J Emerg Med 2016;34:985-8.	Cohort study; included less than 500 patients
Hamel E, Pacouret G, Vincentelli D, et al. Thrombolysis or heparin therapy in massive pulmonary embolism with right ventricular dilation: results from a 128-patient monocenter registry. Chest 2001;120:120-5.	Cohort study; included less than 500 patients
Excluded by Planer (2023) because of high risk of bias	
Iskandar JP, Hariri E, Kanaan C, Kassis N, Kamran H, Sese D, et al. The safety and efficacy of systemic versus catheter-based therapies: application of a prognostic model by a pulmonary embolism response team. J Thromb Thrombolysis. 2022;53(3):616–25.	Cohort study; included less than 500 patients
Nicholas A Barrett, Anthony Byrne ADMH and NR. Management of massive pulmonary embolism: a retrospective single-centre cohort study. Crit Care Study Guid Text Rev Second Ed. 2010;(December):305–19.	Cohort study; included less than 500 patients
Konstantinides S, Tiede N, Geibel A, Olschewski M, Just H, Kasper W. Comparison of alteplase versus heparin for resolution of major pulmonary embolism. Am J Cardiol. 1998;82(8):966–70.	Published before 2000
Nakamura M, Nakanishi N, Yamada N, Sakuma M, Miyahara Y, Okada O, et al. Effectiveness and safety of the thrombolytic therapy for acute pulmonary thromboembolism: Results of a multicenter registry in the Japanese Society of Pulmonary Embolism Research. Int J Cardiol. 2005;99(1):83–9.	Cohort study; included less than 500 patients
Riera-Mestre A, Jiménez D, Muriel A, Lobo JL, Moores L, Yusen RD, et al. Thrombolytic therapy and outcome of patients with an acute symptomatic pulmonary embolism. J Thromb Haemost. 2012;10(5):751–9.	Cohort study; included less than 500 patients
Sekulic I, Dzudovic B, Matijasevic J, Batranovic U, Rusovic S, Mihajlovic M, et al. Ultrasound assisted thrombolysis in intermediate-risk patients with pulmonary thromboembolism. Acta Cardiol. 2020;75(7):623–30.	Cohort study; included less than 500 patients
Zulty M, Saleh N, Hernandez J, Kalaria A, Camire L, Weisman DS. Catheter-Directed Therapy: Outcomes Versus Standard of Care and Evaluation of Current Practice. Am J Med. 2021;134(3):400–4.	Cohort study; included less than 500 patients
Omaygenc DO, Omaygenc MO. thrombolysis and anticoagulation embolism : A retrospective analysis. 2021;	Cohort study; included less than 500 patients

Table of excluded studies from the search strategy

Reference	Reason for exclusion
Agnelli, G. and Becattini, C. and Kirschstein, T. Thrombolysis vs heparin in the treatment of pulmonary embolism: A clinical outcome-based meta-analysis. Archives of Internal Medicine. 2002; 162 (22) :2537-2541	a more recent meta-analysis was included
Wan, S. and Quinlan, D. J. and Agnelli, G. and Eikelboom, J. W. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: A meta-analysis of the randomized controlled trials. Circulation. 2004; 110 (6) :744-749	a more recent meta-analysis was included
Cao, Y. and Zhao, H. and Gao, W. and Wang, Y. and Cao, J. Systematic review and meta-analysis for thrombolysis treatment in patients with	a more recent meta-analysis was included

acute submassive pulmonary embolism. Patient Preference and Adherence. 2014; 8 :275-282	
Chatterjee, S. and Chakraborty, A. and Weinberg, I. and Kadakia, M. and Wilensky, R. L. and Sardar, P. and Kumbhani, D. J. and Mukherjee, D. and Jaff, M. R. and Giri, J. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: A meta-analysis. JAMA. 2014; 311 (23) :2414-2421	a more recent meta-analysis was included
Riera-Mestre, Antoni and Becattini, Cecilia and Giustozzi, Michela and Agnelli, Giancarlo Thrombolysis in hemodynamically stable patients with acute pulmonary embolism: a meta-analysis. Thrombosis research. 2014; 134 (6) :1265-71	a more recent meta-analysis was included
Janz, T. G. Using thrombolytic therapy for life-threatening pulmonary embolism. Journal of Critical Illness. 2003; 18 (3) :102-109	narrative review
Büller, H. R. and Agnelli, G. and Hull, R. D. and Hyers, T. M. and Prins, M. H. and Raskob, G. E. Antithrombotic therapy for venous thromboembolic disease: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004; 126 (3) :401S-428S	conference proceedings
Goldhaber, S. Z. Pulmonary embolism. Lancet. 2004; 363 (9417) :1295-1305	narrative review
Meyer, G. and Sanchez, O. Indications and modalities of fibrinolytic therapy for pulmonary embolism. Sang Thrombose Vaisseaux. 2009; 21 (4) :181-185	narrative review
Meyer, G. Thrombolytic therapy for pulmonary embolism. Journal des Maladies Vasculaires. 2011; 36 :S33-S36	narrative review
Chen, H. and Ren, C. and Chen, H. Thrombolysis versus anticoagulation for the initial treatment of moderate pulmonary embolism: A meta-analysis of randomized controlled trials. Respiratory Care. 2014; 59 (12) :1880-1887	a more recent meta-analysis was included
Liu, Yunfeng and Lu, Youjin and Song, Jian and Li, Dan and Liu, Hongyan and Yang, Jin and Zhao, Hui Recombinant tissue plasminogen activator for hemodynamically stable patients experiencing an acute pulmonary embolism: a meta-analysis. Thrombosis research. 2014; 134 (1) :50-6	a more recent meta-analysis was included
Nakamura, S. and Takano, H. and Kubota, Y. and Asai, K. and Shimizu, W. Impact of the efficacy of thrombolytic therapy on the mortality of patients with acute submassive pulmonary embolism: a meta-analysis. Journal of thrombosis and haemostasis : JTH. 2014; 12 (7) :1086-95	a more recent meta-analysis was included
Konstantinides, S. and Geibel, A. and Heusel, G. and Heinrich, F. and Kasper, W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. New England Journal of Medicine. 2002; 347 (15) :1143-1150	a more recent meta-analysis was included
Kelly, J. and Hunt, B. J. Do anticoagulants improve survival in patients presenting with venous thromboembolism?. Journal of Internal Medicine. 2003; 254 (6) :527-539	narrative review
Aleksic, I. and Kamler, M. and Herold, U. and Massoudy, P. and Jakob, H. G. Surgical treatment for massive pulmonary embolism. Herz. 2005; 30 (4) :269-273	narrative review
Gao, Guang-yuan and Yang, Ping and Liu, Miao and Ding, Mei and Liu, Guo-hui and Tong, Ya-liang and Yang, Chun-yan and Meng, Fan-bo Thrombolysis for acute intermediate-risk pulmonary embolism: A meta-analysis. Thrombosis research. 2015; 136 (5) :932-7	a more recent meta-analysis was included
Marti, C. and John, G. and Konstantinides, S. and Combescur, C. and Sanchez, O. and Lankeit, M. and Meyer, G. and Perrier, A. Systemic	a more recent meta-analysis was included

thrombolytic therapy for acute pulmonary embolism: A systematic review and meta-analysis. European Heart Journal. 2015; 36 (10) :605-614	
Xu, Q. and Huang, K. and Zhai, Z. and Yang, Y. and Wang, J. and Wang, C. Initial thrombolysis treatment compared with anticoagulation for acute intermediate-risk pulmonary embolism: A meta-analysis. Journal of Thoracic Disease. 2015; 7 (5) :810-821	a more recent meta-analysis was included
Vedantham, S. Interventional approaches to acute venous thromboembolism. Seminars in Respiratory and Critical Care Medicine. 2008; 29 (1) :56-65	narrative review
Alcedo, P. E. and García-Perdomo, H. A. and Rojas-Hernandez, C. M. The net benefit of thrombolysis in the management of intermediate risk pulmonary embolism: Systematic review and meta-analysis. eJHaem. 2020; 1 (2) :457-466	a more recent meta-analysis was included
Sharifi, M. and Bay, C. and Skrocki, L. and Rahimi, F. and Mehdipour, M. Moderate pulmonary embolism treated with thrombolysis (from the "mOPETT" Trial). American Journal of Cardiology. 2013; 111 (2) :273-277	Study already included in Planer (2023)
Kucher, N. and Boekstegers, P. and Müller, O. J. and Kupatt, C. and Beyer-Westendorf, J. and Heitzer, T. and Tebbe, U. and Horstkotte, J. and Müller, R. and Blessing, E. and Greif, M. and Lange, P. and Hoffmann, R. T. and Werth, S. and Barmeyer, A. and Härtel, D. and Grünwald, H. and Empen, K. and Baumgartner, I. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014; 129 (4) :479-486	Study already included in Planer (2023)
Meyer, G. and Vicaut, E. and Danays, T. and Agnelli, G. and Becattini, C. and Beyer-Westendorf, J. and Bluhmki, E. and Bouvaist, H. and Brenner, B. and Couturaud, F. and Dellas, C. and Empen, K. and Franca, A. and Galiè, N. and Geibel, A. and Goldhaber, S. Z. and Jimenez, D. and Kozak, M. and Kupatt, C. and Kucher, N. and Lang, I. M. and Lankeit, M. and Meneveau, N. and Pacouret, G. and Palazzini, M. and Petris, A. and Pruszczyk, P. and Rugolotto, M. and Salvi, A. and Schellong, S. and Sebbane, M. and Sobkowicz, B. and Stefanovic, B. S. and Thiele, H. and Torbicki, A. and Verschuren, F. and Konstantinides, S. V. Fibrinolysis for patients with intermediate-risk pulmonary embolism. New England Journal of Medicine. 2014; 370 (15) :1402-1411	Study already included in Planer (2023)
Konstantinides, Stavros V. and Vicaut, Eric and Danays, Thierry and Becattini, Cecilia and Bertoletti, Laurent and Beyer-Westendorf, Jan and Bouvaist, Helene and Couturaud, Francis and Dellas, Claudia and Duerschmied, Daniel and Empen, Klaus and Ferrari, Emile and Galie, Nazzareno and Jimenez, David and Kostrubiec, Maciej and Kozak, Matija and Kupatt, Christian and Lang, Irene M. and Lankeit, Mareike and Meneveau, Nicolas and Palazzini, Massimiliano and Pruszczyk, Piotr and Rugolotto, Matteo and Salvi, Aldo and Sanchez, Olivier and Schellong, Sebastian and Sobkowicz, Bozena and Meyer, Guy Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism. Journal of the American College of Cardiology. 2017; 69 (12) :1536-1544	Study already included in Planer (2023)
D'Auria S, Sezer A, Thoma F, Sharbaugh M, McKibben J, Maholic R, Avgerinos ED, Rivera-Lebron BN, Toma C. Outcomes of catheter-directed thrombolysis vs. standard medical therapy in patients with acute submassive pulmonary embolism. Pulm Circ. 2020 Apr 8;10(1):2045894019898368. doi: 10.1177/2045894019898368. PMID: 32292583; PMCID: PMC7144676.	Study already included in Planer (2023)

Ishisaka Y, Watanabe A, Fujisaki T, Iwagami M, So M, Steiger D, Aoi S, Secemsky EA, Wiley J, Kuno T. Comparison of interventions for intermediate to high-risk pulmonary embolism: A network meta-analysis. Catheter Cardiovasc Interv. 2023 Aug;102(2):249-265. doi: 10.1002/ccd.30745. Epub 2023 Jun 3. PMID: 37269229.	No detailed search strategy
Mathew, D. and Kim, J. and Kosuru, B. P. and Devagudi, D. and Sherif, A. and Shrestha, U. and Bedi, P. Mortality and bleeding associated with the management of sub-massive pulmonary embolism: a systematic review and Bayesian network meta-analysis. Scientific reports. 2023; 13 (1) :7169	search strategy not clear
Kroupa, J. and Buk, M. and Weichet, J. and Malikova, H. and Bartova, L. and Linkova, H. and Ionita, O. and Kozel, M. and Motovska, Z. and Kocka, V. A pilot randomised trial of catheter-directed thrombolysis or standard anticoagulation for patients with intermediate-high risk acute pulmonary embolism. EuroIntervention. 2022; 18 (8) :E639-E646	Study already included in Planer (2023)
Qin, Zhi-qiang and Wang, Chen [Comparison of thrombolysis and anticoagulation in pulmonary thromboembolism: a meta-analysis]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases. 2003; 26 (12) :772-5	article in chinese
Goldhaber, S. Z. Thrombolytic therapy for patients with pulmonary embolism who are hemodynamically stable but have right ventricular dysfunction: Pro. Archives of Internal Medicine. 2005; 165 (19) :2197-2205	opinion article/ commentary
Harris, T. and Meek, S. When should we thrombolyse patients with pulmonary embolism? A systematic review of the literature. Emergency Medicine Journal. 2005; 22 (11) :766-771	narrative review
Konstantinides, S. Pulmonary embolism: Impact of right ventricular dysfunction. Current Opinion in Cardiology. 2005; 20 (6) :496-501	narrative review
Meyer, G. and Sanchez, O. Thrombolysis in pulmonary embolism. Reanimation. 2005; 14 (3) :196-202	narrative review
Wan, S. and Quinlan, D. J. and Agnelli, G. and Eikelboom, J. W. and Elliott, G. and Stevens, S. Review: Thrombolytic treatment does not reduce the risk of recurrent pulmonary embolism and death more than heparin. Evidence-Based Medicine. 2005; 10 (2) :41	narrative review
Wang L. Thrombolytic Therapy for Pulmonary Embolism: Lessons from Recent Clinical Trials. Australasian Journal of Paramedicine. 2005;3:1-6. doi:10.33151/ajp.3.4.341	narrative review
Emmerich, J. and Meyer, G. and Decousus, H. and Agnelli, G. Role of fibrinolysis and interventional therapy for acute venous thromboembolism. Thrombosis and Haemostasis. 2006; 96 (3) :251-257	narrative review
Ramakrishnan, Naresh Thrombolysis is not warranted in submassive pulmonary embolism: a systematic review and meta-analysis. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine. 2007; 9 (4) :357-63	narrative review
Skaf, E. and Beemath, A. and Siddiqui, T. and Janjua, M. and Patel, N. R. and Stein, P. D. Catheter-Tip Embolectomy in the Management of Acute Massive Pulmonary Embolism. American Journal of Cardiology. 2007; 99 (3) :415-420	does not fit the PICO
Worster, Andrew and Smith, Camala and Silver, Shawna and Brown, Michael D. Evidence-based emergency medicine/critically appraised topic. Thrombolytic therapy for submassive pulmonary embolism?. Annals of emergency medicine. 2007; 50 (1) :78-84	does not fit the PICO

Kuo, W. T. and Gould, M. K. and Louie, J. D. and Rosenberg, J. K. and Sze, D. Y. and Hofmann, L. V. Catheter-directed Therapy for the Treatment of Massive Pulmonary Embolism: Systematic Review and Meta-analysis of Modern Techniques. Journal of Vascular and Interventional Radiology. 2009; 20 (11) :1431-1440	does not fit the PICO
Tardy, B. and Venet, C. and Zeni, F. and Coudrot, M. and Guyomarc'h, S. and Mismetti, P. Short term effect of recombinant tissue plasminogen activator in patients with hemodynamically stable acute pulmonary embolism: Results of a meta-analysis involving 464 patients. Thrombosis Research. 2009; 124 (6) :672-677	wrong I, does not fit the PICO
Lankeit, M. and Konstantinides, S. Thrombolysis for pulmonary embolism: Past, present and future. Thrombosis and Haemostasis. 2010; 103 (5) :877-883	narrative review
Kuo, W. T. Endovascular therapy for acute pulmonary embolism. Journal of Vascular and Interventional Radiology. 2012; 23 (2) :167-179	narrative review
Lankeit, Mareike and Konstantinides, Stavros Thrombolytic therapy for submassive pulmonary embolism. Best practice & research. Clinical haematology. 2012; 25 (3) :379-89	review/ study protocol
Tapson, V. F. Thrombolytic therapy in acute pulmonary embolism. Current Opinion in Cardiology. 2012; 27 (6) :585-591	narrative review
Bunwaree, S. and Roffi, M. and Bonvini, J. M. and Noble, S. and Righini, M. and Bonvini, R. F. AngioJet® rheolytic thrombectomy: A new treatment option in cases of massive pulmonary embolism. Interventional Cardiology (London). 2013; 5 (1) :71-87	wrong C
He, C. and Von Segesser, L. K. and Kappetein, P. A. and Mestres, C. A. and Smith, J. A. and Choong, C. K. C. Acute pulmonary embolectomy. European Journal of Cardio-thoracic Surgery. 2013; 43 (6) :1087-1095	narrative review
Heberlein, Wolf E. and Meek, Mollie E. and Saleh, Omar and Meek, James C. and Lensing, Shelly Y. and Culp, William C. New generation aspiration catheter: Feasibility in the treatment of pulmonary embolism. World journal of radiology. 2013; 5 (11) :430-5	case series
Chen, H. and Ren, C. and Chen, H. Thrombolysis versus anticoagulation for the initial treatment of moderate pulmonary embolism: A meta-analysis of randomized controlled trials. Respiratory Care. 2014; 59 (12) :1880-1887	a more recent meta-analysis was included
Engelberger, R. P. and Kucher, N. Ultrasound-assisted thrombolysis for acute pulmonary embolism: A systematic review. European Heart Journal. 2014; 35 (12) :758-764	narrative review
Liu, Yunfeng and Lu, Youjin and Song, Jian and Li, Dan and Liu, Hongyan and Yang, Jin and Zhao, Hui Recombinant tissue plasminogen activator for hemodynamically stable patients experiencing an acute pulmonary embolism: a meta-analysis. Thrombosis research. 2014; 134 (1) :50-6	a more recent meta-analysis was included
Nakamura, S. and Takano, H. and Kubota, Y. and Asai, K. and Shimizu, W. Impact of the efficacy of thrombolytic therapy on the mortality of patients with acute submassive pulmonary embolism: a meta-analysis. Journal of thrombosis and haemostasis : JTH. 2014; 12 (7) :1086-95	wrong I
Konstantinides, S. and Geibel, A. and Kasper, W. Thrombolytic treatment of pulmonary embolism: Life-saving option or unacceptable risk?. Intensivmedizin und Notfallmedizin. 2000; 37 (1) :139-145	narrative review
Arcasoy, Selim M. and Vachani, Anil Local and systemic thrombolytic therapy for acute venous thromboembolism. Clinics in chest medicine. 2003; 24 (1) :73-91	narrative review

Pérez de Llano, L. A. and Baloira Villar, A. and Veres Racamonde, A. and Veiga, F. and Golpe Gómez, R. and Pajuelo Fernández, F. Multicenter, prospective study comparing enoxaparin with unfractionated heparin in the treatment of submassive pulmonary thromboembolism. Archivos de Bronconeumologia. 2003; 39 (8) :341-345	does not fit the PICO
Konstantinides, S. Should thrombolytic therapy be used in patients with pulmonary embolism?. American Journal of Cardiovascular Drugs. 2004; 4 (2) :69-74	narrative review
Madden, B. P. and Sheth, A. and Ho, T. B. L. Thrombolytic therapy for acute proximal pulmonary embolism without significant haemodynamic compromise. Respiratory Medicine Extra. 2006; 2 (1) :34-38	case series
Zhang, Zhu and Zhai, Zhen-guo and Liang, Li-rong and Liu, Fang-fang and Yang, Yuan-hua and Wang, Chen Lower dosage of recombinant tissue-type plasminogen activator (rt-PA) in the treatment of acute pulmonary embolism: a systematic review and meta-analysis. Thrombosis research. 2014; 133 (3) :357-63	wrong I, does not fit the PICO
Brandt, K. and McGinn, K. and Quedado, J. Low-Dose Systemic Alteplase (tPA) for the Treatment of Pulmonary Embolism. Annals of Pharmacotherapy. 2015; 49 (7) :818-824	narrative review
Gao, Guang-yuan and Yang, Ping and Liu, Miao and Ding, Mei and Liu, Guo-hui and Tong, Ya-liang and Yang, Chun-yan and Meng, Fan-bo Thrombolysis for acute intermediate-risk pulmonary embolism: A meta-analysis. Thrombosis research. 2015; 136 (5) :932-7	a more recent meta-analysis was included
Meyer G, Planquette B, Sanchez O. Fibrinolysis for Acute Care of Pulmonary Embolism in the Intermediate Risk Patient. Curr Atheroscler Rep. 2015 Dec;17(12):68. doi: 10.1007/s11883-015-0546-1. PMID: 26486512.	does not fit the PICO
Meyer, G. and Sanchez, O. and Planquette, B. Intermediate-risk pulmonary embolism. Thrombolysis, yes or no?. Reanimation. 2015; 24 (2) :98-103	narrative review
Wärntges, S. and Konstantinides, S. V. Progress in the management of acute pulmonary embolism. Current Opinion in Pulmonary Medicine. 2015; 21 (5) :417-424	narrative review
Xu, Q. and Huang, K. and Zhai, Z. and Yang, Y. and Wang, J. and Wang, C. Initial thrombolysis treatment compared with anticoagulation for acute intermediate-risk pulmonary embolism: A meta-analysis. Journal of Thoracic Disease. 2015; 7 (5) :810-821	a more recent meta-analysis was included
Bajaj, N. S. and Kalra, R. and Arora, P. and Ather, S. and Guichard, J. L. and Lancaster, W. J. and Patel, N. and Raman, F. and Arora, G. and Al Solaiman, F. and Clark, D. T. and Dell'Italia, L. J. and Leesar, M. A. and Davies, J. E. and McGiffin, D. C. and Ahmed, M. I. Catheter-directed treatment for acute pulmonary embolism: Systematic review and single-arm meta-analyses. International Journal of Cardiology. 2016; 225 :128-139	does not fit the PICO
Keeling, W. B. and Leshnower, B. G. and Lasajanak, Y. and Binongo, J. and Guyton, R. A. and Halkos, M. E. and Thourani, V. H. and Lattouf, O. M. Midterm benefits of surgical pulmonary embolectomy for acute pulmonary embolus on right ventricular function. Journal of Thoracic and Cardiovascular Surgery. 2016; 152 (3) :872-878	does not fit the PICO
Teleb, M. and Porres-Aguilar, M. and Anaya-Ayala, J. E. and Rodriguez-Castro, C. and Porres-Muñoz, M. and Mukherjee, D. Potential role of systemic thrombolysis in acute submassive intermediate risk pulmonary embolism: Review and future	narrative review

perspectives. Therapeutic Advances in Cardiovascular Disease. 2016; 10 (2) :103-110	
Bloomer, T. L. and El-Hayek, G. E. and McDaniel, M. C. and Sandvall, B. C. and Liberman, H. A. and Devireddy, C. M. and Kumar, G. and Fong, P. P. and Jaber, W. A. Safety of catheter-directed thrombolysis for massive and submassive pulmonary embolism: Results of a multicenter registry and meta-analysis. Catheterization and Cardiovascular Interventions. 2017; 89 (4) :754-760	does not fit the PICO
Kalra, R. and Bajaj, N. S. and Arora, P. and Arora, G. and Crosland, W. A. and McGiffin, D. C. and Ahmed, M. I. Surgical Embolectomy for Acute Pulmonary Embolism: Systematic Review and Comprehensive Meta-Analyses. Annals of Thoracic Surgery. 2017; 103 (3) :982-990	does not fit the PICO
Kesselman, A. and Kuo, W. T. Catheter-Directed Therapy for Acute Submassive Pulmonary Embolism: Summary of Current Evidence and Protocols. Techniques in Vascular and Interventional Radiology. 2017; 20 (3) :193-196	narrative review
Konstantinides, S. V. and Barco, S. Systemic Thrombolytic Therapy for Acute Pulmonary Embolism: Who Is a Candidate?. Seminars in Respiratory and Critical Care Medicine. 2017; 38 (1) :056-065	narrative review
Li, X. F. and Wan, C. Q. and He, X. G. and Qiu, J. Y. and Li, D. Y. and Sun, Y. X. and Mao, Y. M. Catheter-directed therapy as a treatment for submassive pulmonary embolism: A meta-analysis. Life Sciences. 2017; 188 :17-25	a more recent meta-analysis was included
Lou, B. H. and Wang, L. H. and Chen, Y. A meta-analysis of efficacy and safety of catheter-directed interventions in submassive pulmonary embolism. European review for medical and pharmacological sciences. 2017; 21 (1) :184-198	a more recent meta-analysis was included
Sista, Akhilesh K. and Miller, Larry E. and Kahn, Susan R. and Kline, Jeffrey A. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: Systematic review with meta-analysis. Vascular medicine (London, England). 2017; 22 (1) :37-43	a more recent meta-analysis was included
Perlroth, D. J. and Sanders, G. D. and Gould, M. K. Effectiveness and cost-effectiveness of thrombolysis in submassive pulmonary embolism. Archives of Internal Medicine. 2007; 167 (1) :74-80	does not fit the PICO
Yoo, H. H. B. and Rodrigues, H. and Queluz, T. T. Treatment of pulmonary thromboembolism in patients with systemic blood pressure stability and right ventricular dysfunction. Current Respiratory Medicine Reviews. 2008; 4 (1) :52-56	narrative review
Zamanian, R. T. and Gould, M. K. Effectiveness and cost effectiveness of thrombolysis in patients with acute pulmonary embolism. Current Opinion in Pulmonary Medicine. 2008; 14 (5) :422-426	narrative review
Todd, J. L. and Tapson, V. F. Thrombolytic therapy for acute pulmonary embolism: A critical appraisal. Chest. 2009; 135 (5) :1321-1329	narrative review
Gao, H. and Huang, G. Y. and Ma, L. L. and Wang, L. X. Combined catheter thrombus fragmentation and fibrinolysis for acute pulmonary embolism. Internal Medicine Journal. 2011; 41 (9) :687-691	Case series
Jin, J. and Ding, W. B. and Yuan, R. F. Thrombolytic treatment of acute pulmonary thromboembolism: Comparison between catheter-directed thrombolysis and venous thrombolysis. Journal of Interventional Radiology (China). 2012; 21 (8) :667-671	does not fit the PICO
Steering Committee. Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular	Trial protocol

dysfunction and myocardial injury: rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Am Heart J. 2012 Jan;163(1):33-38.e1. doi: 10.1016/j.ahj.2011.10.003. PMID: 22172434.	
Tafur, A. J. and Shamoun, F. E. and Patel, S. I. and Tafur, D. and Donna, F. and Murad, M. H. Catheter-Directed Treatment of Pulmonary Embolism: A Systematic Review and Meta-Analysis of Modern Literature. Clinical and Applied Thrombosis/Hemostasis. 2017; 23 (7) :821-829	More recent review included
Tapson, V. F. and Friedman, O. Systemic Thrombolysis for Pulmonary Embolism: Who and How. Techniques in Vascular and Interventional Radiology. 2017; 20 (3) :162-174	narrative review
Tromeur, C. and Van Der Pol, L. M. and Couturaud, F. and Klok, F. A. and Huisman, M. V. Therapeutic management of acute pulmonary embolism. Expert Review of Respiratory Medicine. 2017; 11 (8) :641-648	narrative review
Avgerinos, E. D. and Saadeddin, Z. and Abou Ali, A. N. and Fish, L. and Toma, C. and Chaer, M. and Rivera-Lebron, B. N. and Chaer, R. A. A meta-analysis of outcomes of catheter-directed thrombolysis for high- and intermediate-risk pulmonary embolism. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2018; 6 (4) :530-540	More recent review included
Eberle, H. and Lyn, R. and Knight, T. and Hodge, E. and Daley, M. Clinical update on thrombolytic use in pulmonary embolism: A focus on intermediate-risk patients. American Journal of Health-System Pharmacy. 2018; 75 (17) :1275-1285	narrative review
Harvey JJ, Huang S, Uberoi R. Catheter-directed therapies for the treatment of high risk (massive) and intermediate risk (submassive) acute pulmonary embolism. Cochrane Database Syst Rev. 2022 Aug 8;8(8):CD013083. doi: 10.1002/14651858.CD013083.pub2. PMID: 35938605; PMCID: PMC9358724.	More recent review included
Kaymaz, C. and Akbal, Ö Y. and Tanboğa, I. H. and Hakgör, A. and Yilmaz, F. and Öztürk, S. and Poçi, N. and Türkday, S. and Özdemir, N. and Konstantinides, S. Ultrasound-assisted catheter-directed thrombolysis in high-risk and intermediate-high-risk pulmonary embolism: A meta-analysis. Current Vascular Pharmacology. 2018; 16 (2) :179-189	a more recent NMA was included
Loyalka, P. and Ansari, M. Z. and Cheema, F. H. and Miller, C. C. and Rajagopal, S. and Rajagopal, K. Surgical pulmonary embolectomy and catheter-based therapies for acute pulmonary embolism: A contemporary systematic review. Journal of Thoracic and Cardiovascular Surgery. 2018; 156 (6) :2155-2167	included massive PE, wrong P
Riva, Nicoletta and Puljak, Livia and Moja, Lorenzo and Ageno, Walter and Schunemann, Holger and Magrini, Nicola and Squizzato, Alessandro Multiple overlapping systematic reviews facilitate the origin of disputes: the case of thrombolytic therapy for pulmonary embolism. Journal of clinical epidemiology. 2018; 97 :1-13	Does not fit the PICO
Schultz, J. and Andersen, A. and Kabrhel, C. and Nielsen-Kudsk, J. E. Catheter-based therapies in acute pulmonary embolism. EuroIntervention. 2018; 13 (14) :1721-1727	narrative review
Pei, D. T. and Liu, J. and Yaqoob, M. and Ahmad, W. and Bandeali, S. S. and Hamzeh, I. R. and Virani, S. S. and Hira, R. S. and Lakkis, N. M. and Alam, M. Meta-Analysis of Catheter Directed Ultrasound-Assisted Thrombolysis in Pulmonary Embolism. American Journal of Cardiology. 2019; 124 (9) :1470-1477	More recent review included
Pillus, D. and Bruno, E. and Farcy, D. and Vilke, G. M. and Childers, R. Systematic Review: The Role of Thrombolysis in Intermediate-Risk	narrative review

Pulmonary Embolism. Journal of Emergency Medicine. 2019; 57 (4) :517-522	
Alcedo, P. E. and García-Perdomo, H. A. and Rojas-Hernandez, C. M. The net benefit of thrombolysis in the management of intermediate risk pulmonary embolism: Systematic review and meta-analysis. eJHaem. 2020; 1 (2) :457-466	More recent review included
Choi, J. H. and O'Malley, T. J. and Maynes, E. J. and Weber, M. P. and D'Antonio, N. D. and Mellado, M. and West, F. M. and Galanis, T. and Gonsalves, C. F. and Marhefka, G. D. and Awsare, B. K. and Merli, G. J. and Tchantchaleishvili, V. Surgical Pulmonary Embolectomy Outcomes for Acute Pulmonary Embolism. Annals of Thoracic Surgery. 2020; 110 (3) :1072-1080	past niet bij de pico
Duffett L, Castellucci LA, Forgie MA. Pulmonary embolism: update on management and controversies. BMJ. 2020 Aug 5;370:m2177. doi: 10.1136/bmj.m2177. PMID: 32759284.	narrative review
Igneri, L. A. and Hammer, J. M. Systemic Thrombolytic Therapy for Massive and Submassive Pulmonary Embolism. Journal of Pharmacy Practice. 2020; 33 (1) :74-89	More recent review included
Izcovich, A. and Criniti, J. M. and Popoff, F. and Lu, L. and Wu, J. and Ageno, W. and Witt, D. M. and Jaff, M. R. and Schulman, S. and Manja, V. and Verhamme, P. and Rada, G. and Zhang, Y. and Nieuwlaat, R. and Wiercioch, W. and Schünemann, H. J. and Neumann, I. Thrombolytics for venous thromboembolic events: A systematic review with meta-analysis. Blood Advances. 2020; 4 (7) :1539-1553	More recent review included
Kline, J. A. and Hernandez, J. and Hogg, M. M. and Jones, A. E. and Courtney, D. M. and Kabrhel, C. and Nordenholz, K. E. and Diercks, D. B. and Rondina, M. T. and Klinger, J. R. Rationale and methodology for a multicentre randomised trial of fibrinolysis for pulmonary embolism that includes quality of life outcomes. EMA - Emergency Medicine Australasia. 2013; 25 (6) :515-526	Trial protocol
Tapson, V. F. Thrombolytic therapy for acute pulmonary embolism. Seminars in Thrombosis and Hemostasis. 2013; 39 (4) :452-458	Narrative review
Patra, S. and Agrawal, N. and Manjunath, C. N. and Nagesh, C. M. and Srinivas, B. C. and Ravindranath, K. S. and Reddy, B. Thrombolytic therapy in the treatment of acute sub-massive pulmonary embolism: A prospective observational study. Blood Coagulation and Fibrinolysis. 2014; 25 (2) :167-171	Cohot study < 500 patients
Sanchez, O. and Planquette, B. and Meyer, G. Management of massive and submassive pulmonary embolism: Focus on recent randomized trials. Current Opinion in Pulmonary Medicine. 2014; 20 (5) :393-399	Narrative review
Shukla, A. N. and Thakkar, B. and Jayaram, A. A. and Madan, T. H. and Gandhi, G. D. Efficacy and safety of tenecteplase in pulmonary embolism. Journal of Thrombosis and Thrombolysis. 2014; 38 (1) :24-29	Case series
Stein, Paul D. and Dalen, James E. Thrombolytic therapy for acute pulmonary embolism: when do the benefits exceed the risks?. The American journal of medicine. 2014; 127 (11) :1031-1032	narrative review
Avgerinos, E. D. and Chaer, R. A. Catheter-directed interventions for acute pulmonary embolism. Journal of Vascular Surgery. 2015; 61 (2) :559-565	Study included by Paner (2023)
Stewart, L. K. and Peitz, G. W. and Nordenholz, K. E. and Courtney, D. M. and Kabrhel, C. and Jones, A. E. and Rondina, M. T. and Diercks, D. B. and Klinger, J. R. and Kline, J. A. Contribution of fibrinolysis to the physical component summary of the SF-36 after acute submassive	Does not fit the PICO

pulmonary embolism. Journal of Thrombosis and Thrombolysis. 2015; 40 (2) :161-166	
Ucar, Elif Yilmazel and Akgun, Metin and Araz, Omer and Tas, Hakan and Kerget, Bugra and Meral, Mehmet and Kaynar, Hasan and Saglam, Leyla Comparison of LMWH versus UFH for hemorrhage and hospital mortality in the treatment of acute massive pulmonary thromboembolism after thrombolytic treatment : randomized controlled parallel group study. Lung. 2015; 193 (1) :121-7	Does not fit the PICO
Vedantham, S. Interventional therapy for venous thromboembolism. Journal of Thrombosis and Haemostasis. 2015; 13 :S245-S251	narrative review
Bradford, M. A. and Lindenauer, P. K. and Walkey, A. J. Practice patterns and complication rates of thrombolysis for pulmonary embolism. Journal of Thrombosis and Thrombolysis. 2016; 42 (3) :313-321	Analysis was stratified by vasopressor use
Sista, Akhilesh K. and Goldhaber, Samuel Z. and Vedantham, Suresh and Kline, Jeffrey A. and Kuo, William T. and Kahn, Susan R. and Kabrhel, Christopher and McLaughlin, Vallerie V. and White, Sarah B. and Kim, Nick H. and Gray, Michael and Simon, Marc A. and Benenati, James F. and Misra, Sanjay and Sterling, Keith M. and Kee, Stephen T. and Konstantinides, Stavros V. and Jaff, Michael R. and Kearon, Clive Research Priorities in Submassive Pulmonary Embolism: Proceedings from a Multidisciplinary Research Consensus Panel. Journal of vascular and interventional radiology : JVIR. 2016; 27 (6) :787-94	Not original data included
Rodriguez, D. and Jerjes-Sanchez, C. and Fonseca, S. and Garcia-Toto, R. and Martinez-Alvarado, J. and Panneflek, J. and Ortiz-Ledesma, C. and Nevarez, F. Thrombolysis in massive and submassive pulmonary embolism during pregnancy and the puerperium: a systematic review. Journal of Thrombosis and Thrombolysis. 2020; 50 (4) :929-941	More recent review included
Tice C, Seigerman M, Fiorilli P, Pugliese SC, Khandhar S, Giri J, Kobayashi T. Management of Acute Pulmonary Embolism. Curr Cardiovasc Risk Rep. 2020;14(12):24. doi: 10.1007/s12170-020-00659-z. Epub 2020 Oct 6. PMID: 33042325; PMCID: PMC7538277.	narrative review
Wu, J. and Chen, H. and Yu, Y. and Peng, L. and Li, J. and Liang, H. and Ba, M. and Ruan, H. and Hong, C. Feasibility of ultrasound-assisted catheter-directed thrombolysis for submassive pulmonary embolism: A meta-analysis of case series. Clinical Respiratory Journal. 2020; 14 (5) :430-439	Meta-analysis of case series
Amini, S. and Bakhshandeh, H. and Mosaed, R. and Abtahi, H. and Sadeghi, K. and Mojtahedzadeh, M. Efficacy and Safety of Different Dosage of Recombinant Tissue-type Plasminogen Activator (rt-PA) in the Treatment of Acute Pulmonary Embolism: A Systematic Review and Meta-analysis. Iranian Journal of Pharmaceutical Research. 2021; 20 (2) :441-454	Does not fit the PICO
Bishay, V. L. and Adenikinju, O. and Todd, R. FlowTriever Retrieval System for the treatment of pulmonary embolism: overview of its safety and efficacy. Expert Review of Medical Devices. 2021; 18 (11) :1039-1048	Does not fit the PICO
Castillo-Perez, M. and Jerjes-Sánchez, C. and Rodríguez, D. and Paredes-Vazquez, J. G. and Panneflek, J. and Vazquez-Guajardo, M. Clinical outcomes of very elderly patients treated with ultrasound-assisted catheter-directed thrombolysis for pulmonary embolism: a systematic review. Journal of Thrombosis and Thrombolysis. 2021; 52 (1) :260-271	Does not fit the PICO

Madathil, R., Anagnostakos, J., Pereira, G. et al. Current Management of Acute Pulmonary Embolism. Curr Surg Rep 9, 16 (2021). https://doi.org/10.1007/s40137-021-00293-7	narrative review
Nguyen PC, Stevens H, Peter K, McFadyen JD. Submassive Pulmonary Embolism: Current Perspectives and Future Directions. J Clin Med. 2021 Jul 30;10(15):3383. doi: 10.3390/jcm10153383. PMID: 34362166; PMCID: PMC8347177.	narrative review
Zuo Z, Yue J, Dong BR, Wu T, Liu GJ, Hao Q. Thrombolytic therapy for pulmonary embolism. Cochrane Database Syst Rev. 2021 Apr 15;4(4):CD004437. doi: 10.1002/14651858.CD004437.pub6. PMID: 33857326; PMCID: PMC8092433.	More recent review included
Chandra, V. M. and Khaja, M. S. and Kryger, M. C. and Sista, A. K. and Wilkins, L. R. and Angle, J. F. and Sharma, A. M. Mechanical aspiration thrombectomy for the treatment of pulmonary embolism: A systematic review and meta-analysis. Vascular Medicine (United Kingdom). 2022; 27 (6) :574-584	More recent review included
Chopard, R. and Meneveau, N. and Ecarnot, F. Catheter-based therapy for acute pulmonary embolism: An overview of current evidence. Archives of Cardiovascular Diseases. 2022; 115 (6) :397-405	narrative review
Freund, Y. and Cohen-Aubart, F. and Bloom, B. Acute Pulmonary Embolism: A Review. JAMA. 2022; 328 (13) :1336-1345	narrative review
Harvey JJ, Huang S, Uberoi R. Catheter-directed therapies for the treatment of high risk (massive) and intermediate risk (submassive) acute pulmonary embolism. Cochrane Database Syst Rev. 2022 Aug 8;8(8):CD013083. doi: 10.1002/14651858.CD013083.pub2. PMID: 35938605; PMCID: PMC9358724.	narrative review
Ismayl, Mahmoud and Machanahalli Balakrishna, Akshay and Aboeata, Ahmed and Gupta, Tanush and Young, Michael N. and Altin, S. Elissa and Aronow, Herbert D. and Goldsweig, Andrew M. Meta-Analysis Comparing Catheter-Directed Thrombolysis Versus Systemic Anticoagulation Alone for Submassive Pulmonary Embolism. The American journal of cardiology. 2022; 178 :154-162	wrong C
Olanipekun, Titilope and Abe, Temidayo and Effoe, Valery and Chris-Olaiya, Abimbola and Biney, Isaac and Guru, Pramod and Ritchie, Charles and Sanghavi, Devang Utilization trends and outcomes of catheter-directed thrombolysis for pulmonary embolism in the US by race/ethnicity. Journal of thrombosis and thrombolysis. 2022; 54 (4) :675-685	does not fit the PICO
Pan, Q. and Gao, H. and Wang, Y. and Chen, Q. Comparison of Efficacy and Safety between Thrombolysis Plus Anticoagulation vs. Anticoagulation Alone for the Treatment of Acute Submassive Pulmonary Embolism: A Systematic Review and Meta-analysis. Current Vascular Pharmacology. 2022; 20 (6) :491-500	More recent review included
Pasha, A. K. and Siddiqui, M. U. and Siddiqui, M. D. and Ahmed, A. and Abdullah, A. and Riaz, I. and Murad, M. H. and Bjarnason, H. and Wysokinski, W. E. and McBane, R. D. Catheter directed compared to systemically delivered thrombolysis for pulmonary embolism: a systematic review and meta-analysis. Journal of Thrombosis and Thrombolysis. 2022; 53 (2) :454-466	More recent review included
Kabrhel, C. and Ali, A. and Choi, J. G. and Hur, C. Systemic Thrombolysis, Catheter-Directed Thrombolysis, and Anticoagulation for Intermediate-risk Pulmonary Embolism: A Simulation Modeling Analysis. Academic Emergency Medicine. 2017; 24 (10) :1235-1243	No original study/data
Kosova EC, Desai KR, Schimmel DR. Endovascular Management of Massive and Submassive Acute Pulmonary Embolism: Current Trends	narrative review

in Risk Stratification and Catheter-Directed Therapies. Curr Cardiol Rep. 2017 Jun;19(6):54. doi: 10.1007/s11886-017-0864-8. PMID: 28466280.	
Mangi, Muhammad A. and Rehman, Hiba and Bansal, Vikas and Zuberi, Omer Ultrasound Assisted Catheter-Directed Thrombolysis of Acute Pulmonary Embolism: A Review of Current Literature. Cureus. 2017; 9 (7) :e1492	narrative review
Teleb, M. and Porres-Aguilar, M. and Rivera-Lebron, B. and Ngamdu, K. S. and Botrus, G. and Anaya-Ayala, J. E. and Mukherjee, D. Ultrasound-Assisted Catheter-Directed Thrombolysis: A Novel and Promising Endovascular Therapeutic Modality for Intermediate-Risk Pulmonary Embolism. Angiology. 2017; 68 (6) :494-501	narrative review
Avgerinos, E. D. and Mohapatra, A. and Rivera-Lebron, B. and Toma, C. and Kabrhel, C. and Fish, L. and Lacomis, J. and Ocak, I. and Chaer, R. A. Design and rationale of a randomized trial comparing standard versus ultrasound-assisted thrombolysis for submassive pulmonary embolism. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2018; 6 (1) :126-132	Trial protocol
Furfaro, D. and Stephens, R. S. and Streiff, M. B. and Brower, R. Catheter-directed thrombolysis for intermediate-risk pulmonary embolism. Annals of the American Thoracic Society. 2018; 15 (2) :134-144	More recent review included
Lozier, J. N. and Elinoff, J. M. and Suffredini, A. F. and Rosing, D. R. and Sidenko, S. and Sherry, R. M. and Metwalli, A. R. and Sachdev, V. and Danner, R. L. and Chang, R. Low-dose, short course alteplase treatment of submassive pulmonary embolism: A case series from the National Institutes of Health Clinical Center. Blood Coagulation and Fibrinolysis. 2018; 29 (8) :701-707	case series
Tapson, V. F. and Sterling, K. and Jones, N. and Elder, M. and Tripathy, U. and Brower, J. and Maholic, R. L. and Ross, C. B. and Natarajan, K. and Fong, P. and Greenspon, L. and Tamaddon, H. and Piracha, A. R. and Engelhardt, T. and Katopodis, J. and Marques, V. and Sharp, A. S. P. and Piazza, G. and Goldhaber, S. Z. A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism: The OPTALYSE PE Trial. JACC: Cardiovascular Interventions. 2018; 11 (14) :1401-1410	Dose comparison trial
Zhang, L. Y. and Gao, B. A. and Jin, Z. and Xiang, G. M. and Gong, Z. and Zhang, T. T. and Lu, H. F. and Wang, Y. Q. and Gong, Y. and Lu, C. and Huang, W. L. Clinical efficacy of low dose recombinant tissue-type plasminogen activator for the treatment of acute intermediate-risk pulmonary embolism. Saudi Medical Journal. 2018; 39 (11) :1090-1095	Included in Planer (2023)
Zhao, T. and Ni, J. and Hu, X. and Wang, Y. and Du, X. The Efficacy and Safety of Intermittent Low-Dose Urokinase Thrombolysis for the Treatment of Senile Acute Intermediate-High-Risk Pulmonary Embolism: A Pilot Trial. Clinical and Applied Thrombosis/Hemostasis. 2018; 24 (7) :1067-1072	Comparison between two agents for thrombolysis
Barco, Stefano and Russo, Mariaconcetta and Vicaut, Eric and Becattini, Cecilia and Bertoletti, Laurent and Beyer-Westendorf, Jan and Bouvaist, Helene and Couturaud, Francis and Danays, Thierry and Dellas, Claudia and Duerschmied, Daniel and Empen, Klaus and Ferrari, Emile and Galie, Nazzareno and Jimenez, David and Klok, Frederikus A. and Kostrubiec, Maciej and Kozak, Matija and Kupatt, Christian and Lang, Irene M. and Lankeit, Mareike and Meneveau, Nicolas and Palazzini, Massimiliano and Pruszczyk, Piotr and	No comparison

Rugolotto, Matteo and Salvi, Aldo and Sanchez, Olivier and Schellong, Sebastian and Sobkowicz, Bozena and Meyer, Guy and Konstantinides, Stavros V. Incomplete echocardiographic recovery at 6 months predicts long-term sequelae after intermediate-risk pulmonary embolism. A post-hoc analysis of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Clinical research in cardiology : official journal of the German Cardiac Society. 2019; 108 (7) :772-778	
Bin, H. and Binxia, S. and Xufeng, C. and Lin, L. and Jinsong, Z. Effects of the combination of alteplase or urokinase with low molecular weight heparin anticoagulant therapy in the treatment of elderly patients with acute submassive pulmonary embolism. Acta Medica Mediterranea. 2019; 35 (3) :1287-1292	does not fit the PICO
Taslakian B, Li C, Goldhaber SZ, Mikkelsen KZ, Horowitz JM, Kabrhel C, Barnes GD, Sista AK. How the Results of a Randomized Trial of Catheter-Directed Thrombolysis Versus Anticoagulation alone for Submassive Pulmonary Embolism Would Affect Patient and Physician Decision Making: Report of an Online Survey. J Clin Med. 2019 Feb 7;8(2):215. doi: 10.3390/jcm8020215. PMID: 30736480; PMCID: PMC6406864.	does not fit the PICO
Belsky J, Warren P, Stanek J, Kumar R. Catheter-directed thrombolysis for submassive pulmonary embolism in children: A case series. Pediatr Blood Cancer. 2020 Apr;67(4):e28144. doi: 10.1002/pbc.28144. Epub 2019 Dec 25. PMID: 31876109.	Case series in children
D'Auria S, Sezer A, Thoma F, Sharbaugh M, McKibben J, Maholic R, Avgerinos ED, Rivera-Lebron BN, Toma C. Outcomes of catheter-directed thrombolysis vs. standard medical therapy in patients with acute submassive pulmonary embolism. Pulm Circ. 2020 Apr 8;10(1):2045894019898368. doi: 10.1177/2045894019898368. PMID: 32292583; PMCID: PMC7144676.	Included in Planer (2023)
Geller, B. J. and Adusumalli, S. and Pugliese, S. C. and Khatana, S. A. M. and Nathan, A. and Weinberg, I. and Jaff, M. R. and Kobayashi, T. and Mazurek, J. A. and Khandhar, S. and Yang, L. and Groeneveld, P. W. and Giri, J. S. Outcomes of catheter-directed versus systemic thrombolysis for the treatment of pulmonary embolism: A real-world analysis of national administrative claims. Vascular Medicine (United Kingdom). 2020; 25 (4) :334-340	More recent review included
Layman, S. N. and Guidry, T. J. and Gillion, A. R. Low-Dose Alteplase for the Treatment of Submassive Pulmonary Embolism: A Case Series. Journal of Pharmacy Practice. 2020; 33 (5) :708-711	case series
Pietrasik A, Gąsecka A, Szarpak Ł, Pruc M, Kopiec T, Darocha S, Banaszkiewicz M, Niewada M, Grabowski M, Kurzyna M. Catheter-Based Therapies Decrease Mortality in Patients With Intermediate and High-Risk Pulmonary Embolism: Evidence From Meta-Analysis of 65,589 Patients. Front Cardiovasc Med. 2022 Jun 16;9:861307. doi: 10.3389/fcvm.2022.861307. PMID: 35783825; PMCID: PMC9243366.	More recent review included
Siordia JA, Kaur A. Catheter-directed Thrombolysis versus Systemic Anticoagulation for Submassive Pulmonary Embolism: A Meta-Analysis. Curr Cardiol Rev. 2022;18(1):112-117. doi: 10.2174/1573403X17666210603114116. PMID: 34082686; PMCID: PMC9241122.	narrative review
Alsamman, M. and Choudhry, A. M. and AlSaadi, A. M. and Prashad, R. Ultrasound-Accelerated Catheter-Directed Thrombolysis. Cardiology Research. 2023; 14 (3) :161-166	narrative review
Farmakis, I. T. and Keller, K. and Barco, S. and Konstantinides, S. V. and Hobohm, L. From acute pulmonary embolism to post-pulmonary	narrative review

embolism sequelae: Functional and hemodynamic implications. Vasa - European Journal of Vascular Medicine. 2023; 52 (1) :29-37	
Iannaccone, M. and Franchin, L. and Russo, F. and Botti, G. and Castellano, D. and Montorfano, M. and Boccuzzi, G. and Mamas, M. A. and Chieffo, A. Mortality across treatment strategies in intermediate-to-high risk pulmonary embolism in the modern era: A meta-analysis of observational studies and RCTs. International journal of cardiology. 2023; :131127	unclear/incomplete search strategy (interventional (CDT) versus medical therapy), majority observational studies
Milioglou, I. and Farmakis, I. and Wazirali, M. and Ajluni, S. and Khawaja, T. and Chatuverdi, A. and Giannakoulas, G. and Shishehbor, M. and Li, J. Percutaneous thrombectomy in patients with intermediate- and high-risk pulmonary embolism and contraindications to thrombolytics: a systematic review and meta-analysis. Journal of Thrombosis and Thrombolysis. 2023; 55 (2) :228-242	Does not fit the PICO
Murguia AR, Mukherjee D, Ojha C, Rajachandran M, Siddiqui TS, Nickel NP. Reduced-Dose Thrombolysis in Acute Pulmonary Embolism A Systematic Review. Angiology. 2024 Mar;75(3):208-218. doi: 10.1177/00033197231167062. Epub 2023 Apr 15. PMID: 37060258.	narrative review
Pietrasik, A. and Gasecka, A. and Kotulecki, A. and Karolak, P. and Araszkiewicz, A. and Darocha, S. and Grabowski, M. and Kurzyna, M. Catheter-directed therapy to treat intermediate-and high-risk pulmonary embolism: Personal experience and review of the literature. Cardiology Journal. 2023; 30 (3) :462-472	narrative review
Planer, D. and Yanko, S. and Matok, I. and Paltiel, O. and Zmiro, R. and Rotshild, V. and Amir, O. and Elbaz-Greener, G. and Raccah, B. H. Catheter-directed thrombolysis compared with systemic thrombolysis and anticoagulation in patients with intermediate- or high-risk pulmonary embolism: systematic review and network meta-analysis. CMAJ. Canadian Medical Association Journal. 2023; 195 (24) :E833-E843	does not fit the PICO
Meng, Y. and Zhang, J. and Ma, Q. and Qin, H. and Zhang, B. and Pang, H. and Yin, Q. and Tian, H. Pulmonary Interventional Therapy for Acute Massive and Submassive Pulmonary Embolism in Cases Where Thrombolysis Is Contraindicated. Annals of Vascular Surgery. 2020; 64 :169-174	Massive PE
Piazza, G. and Sterling, K. M. and Tapson, V. F. and Ouriel, K. and Sharp, A. S. P. and Liu, P. Y. and Goldhaber, S. Z. One-Year Echocardiographic, Functional, and Quality of Life Outcomes After Ultrasound-Facilitated Catheter-Based Fibrinolysis for Pulmonary Embolism. Circulation: Cardiovascular Interventions. 2020; 13 (8) :E009012	Wrong C
Avgerinos, E. D. and Jaber, W. and Lacomis, J. and Markel, K. and McDaniel, M. and Rivera-Lebron, B. N. and Ross, C. B. and Sechrist, J. and Toma, C. and Chaer, R. and Gladwin, M. and Lamberty, P. and Kabrhel, C. and Klein, A. J. and Makaroun, M. S. and Miller, C. E. and Mohapatra, A. and Phelos, H. and Sachdeva, R. and Al-Khoury, G. and Madigan, M. and Liang, N. and Fish, L. and Phelos, H. and Sheline, J. and Brimmeier, J. Randomized Trial Comparing Standard Versus Ultrasound-Assisted Thrombolysis for Submassive Pulmonary Embolism: The SUNSET sPE Trial. JACC: Cardiovascular Interventions. 2021; 14 (12) :1364-1373	wrong C
Herzig, Matthew and Khandhar, Sameer and Palevsky, Harold and Fritz, Jason and Mehta, Mili and Matthai, William Intermediate-Term Outcomes for Patients with Submassive Pulmonary Embolism	Case series

Treated With Catheter-Directed Thrombolysis. The Journal of invasive cardiology. 2021; 33 (12) :E949-E953	
Lin DS, Lin YS, Wu CK, Lin HH, Lee JK. Midterm Prognosis of Patients With Pulmonary Embolism Receiving Catheter-Directed Thrombolysis or Systemic Thrombolysis: A Nationwide Population-Based Study. J Am Heart Assoc. 2021 Apr 6;10(7):e019296. doi: 10.1161/JAHA.120.019296. Epub 2021 Mar 31. PMID: 33787288; PMCID: PMC8174309.	Case series
Maturana MA, Seitz MP, Pour-Ghaz I, Ibebuogu UN, Khouzam RN. Invasive Strategies for the Treatment of Pulmonary Embolism. Where Are We in 2020? Curr Probl Cardiol. 2021 Mar;46(3):100650. doi: 10.1016/j.cpcardiol.2020.100650. Epub 2020 Jul 22. PMID: 32839040.	narrative review
Michaud, E. and Pan, M. and Aggarwal, V. Catheter-based therapies in acute and chronic pulmonary embolism. Current Opinion in Cardiology. 2021; 36 (6) :704-710	narrative review
Sulimov, D. S. and Freund, A. and Thiele, H. Catheter-directed therapy in pulmonary embolism. Herz. 2021; 46 (5) :399-405	narrative review
Yilmaz, Emine Serap and Uzun, Oguz Low-dose thrombolysis for submassive pulmonary embolism. Journal of investigative medicine : the official publication of the American Federation for Clinical Research. 2021; 69 (8) :1439-1446	Case series
Al-Khadra Y, Missula V, Al-Bast B, Singanallur P, Al Tamimi R, Albast N, Abdu M, Deshpande R, Salih M, White P, Shishehbor MH, Hafiz AM. Outcomes of Mechanical Thrombectomy Compared With Systemic Thrombolysis in Pulmonary Embolism: A Comprehensive Evaluation From the National Inpatient Sample Database. J Endovasc Ther. 2022 Dec 2:15266028221138020. doi: 10.1177/15266028221138020. Epub ahead of print. PMID: 36461672.	Does not fit the PICO
Klok, F. A. and Piazza, G. and Sharp, A. S. P. and Ní Ainle, F. and Jaff, M. R. and Chauhan, N. and Patel, B. and Barco, S. and Goldhaber, S. Z. and Kucher, N. and Lang, I. M. and Schmidtmann, I. and Sterling, K. M. and Becker, D. and Martin, N. and Rosenfield, K. and Konstantinides, S. V. Ultrasound-facilitated, catheter-directed thrombolysis vs anticoagulation alone for acute intermediate-high-risk pulmonary embolism: Rationale and design of the HI-PEITHO study. American Heart Journal. 2022; 251 :43-53	study design description trial protocol description
Krishnan, A. M. and Gadela, N. V. and Ramanathan, R. and Jha, A. and Perkins, M. E. and Metersky, M. L. A Comparative Analysis of Catheter Directed Thrombolysis with Anticoagulation Alone or Systemic tPA in Acute Pulmonary Embolism with Cor Pulmonale. Journal of Intensive Care Medicine. 2022; 37 (10) :1336-1343	Included in Planer (2023)
Kroupa, J. and Buk, M. and Weichet, J. and Malikova, H. and Bartova, L. and Linkova, H. and Ionita, O. and Kozel, M. and Motovska, Z. and Kocka, V. A pilot randomised trial of catheter-directed thrombolysis or standard anticoagulation for patients with intermediate-high risk acute pulmonary embolism. EuroIntervention. 2022; 18 (8) :E639-E646	Included in Planer (2023)
Sadeghipour, Parham and Jenab, Yaser and Moosavi, Jamal and Hosseini, Kaveh and Mohebbi, Bahram and Hosseinsabet, Ali and Chatterjee, Saurav and Pouraliakbar, Hamidreza and Shirani, Shapour and Shishehbor, Mehdi H. and Alizadehasl, Azin and Farrashi, Melody and Rezvani, Mohammad Ali and Rafiee, Farnaz and Jalali, Arash and Rashedi, Sina and Shafe, Omid and Giri, Jay and Monreal, Manuel and Jimenez, David and Lang, Irene and Maleki, Majid and	Included by Planer (2023)

Goldhaber, Samuel Z. and Krumholz, Harlan M. and Piazza, Gregory and Bikdeli, Behnood Catheter-Directed Thrombolysis vs Anticoagulation in Patients With Acute Intermediate-High-risk Pulmonary Embolism: The CANARY Randomized Clinical Trial. JAMA cardiology. 2022; 7 (12) :1189-1197	
Sanchez, O. and Charles-Nelson, A. and Ageno, W. and Barco, S. and Binder, H. and Chatellier, G. and Duerschmied, D. and Empen, K. and Ferreira, M. and Girard, P. and Huisman, M. V. and Jiménez, D. and Katsahian, S. and Kozak, M. and Lankeit, M. and Meneveau, N. and Pruszczyk, P. and Petris, A. and Righini, M. and Rosenkranz, S. and Schellong, S. and Stefanovic, B. and Verhamme, P. and De Wit, K. and Vicaut, E. and Zirlik, A. and Konstantinides, S. V. and Meyer, G. Reduced-Dose Intravenous Thrombolysis for Acute Intermediate-High-risk Pulmonary Embolism: Rationale and Design of the Pulmonary Embolism International THrOmbolysis (PEITHO)-3 trial. Thrombosis and Haemostasis. 2022; 122 (5) :857-866	description of study design
Elmoghrabi, Adel and Shafi, Irfan and Abdelrahman, Ahmed and Osman, Heba and Manasrah, Nouraldeen and Zghouzi, Mohamed and Halboni, Adnan and Patino, Skarlet and Patel, Neel N. and Hakim, Zaher and Gardi, Delair and Lakkis, Nasser and Alraies, M. Chadi Outcomes of Catheter-Based Pulmonary Artery Embolectomy in Patients With Sub-Massive to Massive Pulmonary Embolism. Cureus. 2023; 15 (2) :e34877	retrospective case series
Götzinger F, Lauder L, Sharp ASP, Lang IM, Rosenkranz S, Konstantinides S, Edelman ER, Böhm M, Jaber W, Mahfoud F. Interventional therapies for pulmonary embolism. Nat Rev Cardiol. 2023 Oct;20(10):670-684. doi: 10.1038/s41569-023-00876-0. Epub 2023 May 12. PMID: 37173409; PMCID: PMC10180624.	narrative review

Literature search strategy

Richtlijn: Cluster antitrombotisch beleid	
Uitgangsvraag: Wat is de optimale behandeling van patiënten met acute intermediate-high risk longembolieën?	
Database(s): Ovid/Medline, Embase	Datum:5-7-2023
Periode: 2000-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende concepten: Pulmonary embolism AND intermediate high-risk patients AND hemodynamic monitoring, reperfusion, thrombolysis, embolectomy, fibrinolysis or thrombectomy Alle sleutelartikelen worden gevonden. In afstemming met de adviseur wordt afgesproken alleen de SRs en RCTs aan te bieden in Rayyan.	
Te gebruiken voor richtlijnen tekst: In de databases Embase.com en Ovid/Medline is op 5-7-2023 met relevante zoektermen gezocht naar systematische reviews en RCT's over de optimale behandeling van patiënten met intermediate-high risk longembolieën. De literatuurzoekactie leverde 520 unieke treffers op.	

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	253	123	277
RCTs	205	144	243
Observationele studies			
Totaal	458	267	520

Zoekstrategie

Embase

No.	Query	Results
#21	#16 AND #20 sleutelartikelen gevonden	3
#20	#17 OR #18 OR #19 sleutelartikelen	3
#19	konstantinides AND 2002 AND pulmonary AND embolism AND submassive	1
#18	'randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism' AND kucher AND [2014]/py	1
#17	'fibrinolysis for patients with intermediate-risk pulmonary embolism' AND [2014]/py AND meyer	1
#16	#14 OR #15	458
#15	#8 AND #10 NOT #14 RCT	205
#14	#8 AND #9 SR	253
#10	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1839814
#9	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#8	#7 AND [2000-2023]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal	4429

	experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	
#7	#5 AND #6	8326
#6	'high risk patient'/exp OR 'high risk population'/exp OR 'medium risk population'/exp OR 'medium risk patient'/exp OR 'intermediate risk patient'/exp OR 'moderate risk patient'/exp OR 'moderate risk population'/exp OR intermediate:ti,ab,kw OR 'high* risk*':ti,ab,kw OR submassive:ti,ab,kw OR moderate:ti,ab,kw OR severe:ti,ab,kw OR acute:ti,ab,kw OR 'bad risk':ti,ab,kw	5085027
#5	#1 AND #4	15846
#4	#2 OR #3	460353
#3	'hemodynamic monitoring'/exp OR 'lidco':ti,ab,kw OR 'haemodynamic monitoring':ti,ab,kw OR 'hemodynamic monitoring':ti,ab,kw	80925
#2	'systemic thrombolysis'/exp OR 'reperfusion'/exp OR 'blood clot lysis'/exp OR 'percutaneous catheter'/exp OR 'embolectomy'/exp OR 'fibrinolysis'/exp OR 'thrombectomy'/exp OR 'thrombectom*':ti,ab,kw OR 'fibrin degradation':ti,ab,kw OR 'fibrin splitting':ti,ab,kw OR fibrinolytic*:ti,ab,kw OR fibrinolys*:ti,ab,kw OR 'pulmonary embolectomy'/exp OR (((lung OR pulmonar*) NEAR/3 embolectom*):ti,ab,kw) OR 'percutaneous catheter':ti,ab,kw OR reperfusion:ti,ab,kw OR 'clot lysis':ti,ab,kw OR 'systemic thromboly*':ti,ab,kw	383840
#1	'lung embolism'/exp/mj OR (((lung OR pulmonar*) NEAR/3 (microembolism* OR embolism* OR thromboembolism* OR 'micro embolism*' OR 'thrombo embolism*')):ti,ab,kw)	86045

Ovid/Medline

#	Searches	Results
12	(8 and 10) not 11 RCT	144
11	8 and 9 SR	123
10	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1625962
9	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data	678494

	extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	
8	7 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	2011
7	limit 6 to yr="2000 -Current"	2156
6	4 and 5	2597
5	(intermediate or high* risk* or submassive or moderate or severe or acute or bad risk).ti,ab,kf.	3506921
4	1 and (2 or 3)	5103
3	exp Hemodynamic Monitoring/ or lidco.ti,ab,kf. or haemodynamic monitoring.ti,ab,kf. or hemodynamic monitoring.ti,ab,kf.	4542
2	exp Thrombolytic Therapy/ or exp Reperfusion/ or exp fibrinolysis/ or exp Thrombectomy/ or exp Embolectomy/ or ((lung or pulmonar*) adj3 embolectom*).ti,ab,kf. or percutaneous catheter.ti,ab,kf. or reperfusion.ti,ab,kf. or clot lysis.ti,ab,kf. or systemic thromboly*.ti,ab,kf.	158402
1	exp Pulmonary Embolism/ or ((lung or pulmonar*) adj3 (microembolism* or embolism* or thromboembolism* or micro embolism* or thrombo embolism*)).ti,ab,kf.	64335

Zoekstrategie Monitoring

Onderwerp	Monitoring van patiënten met een acute intermediair-hoog risico longembolie
Zoekstrategie	("Pulmonary Embolism" [MeSH Terms] OR "pulmonary embolism" [title/abstract] OR "pulmonary embolism" [tw] OR "Venous Thromboembolism"[Mesh] OR "deep vein thrombosis" [tiab] OR "deep vein thrombosis" [tw] OR "Venous Thromboembolism"[Mesh] OR "venous thromboembolism" [tiab] OR "venous thromboembolism" [tw] OR "blood clot" [tiab:~3]) AND ("vital sign monitoring" [tiab] OR "vital sign monitoring" [tw] OR "non-invasive monitoring" [tiab] OR "non-invasive monitoring" [tw] OR "Critical Care"[Mesh] OR step-down [tw] OR "intermediate care" [tw] OR "high dependency" [tw] OR "coronary care" [tw] OR "discharge" [tw] AND clinical study [Filter])
Opbrengst	Geen

Module 6 Behandeling buikvene trombose

Autorisatie en geldigheid

Autorisatiedatum:	*pending*
Eerstvolgende beoordeling actualiteit	volgende cyclus binnen het cluster Antitrombotisch beleid
Geautoriseerd door:	*pending*
Belangrijkste wijzigingen t.o.v. vorige versie:	n.v.t., het betreft een nieuwe module
Herbevestiging:	n.v.t.
Regiehouder:	Nederlandse Internisten Vereniging

Uitgangsvraag

Wat is de optimale antistollingsbehandeling voor patiënten met acute buikvenetrombose?

Introduction

Patients with acute symptoms of splanchnic vein thrombosis (SVT, thrombosis of mesenteric vein, portal vein, splenic vein, and/or hepatic veins) are treated with anticoagulants. Treatment with anticoagulants seems beneficial for prevention of recurrent thrombosis, bleeding and development of portal hypertension (Candeloro, 2022; Valeriani, 2021 and Valeriani, 2021). Traditionally vitamin K antagonists (VKA) or low molecular weight heparins (LMWH) have been described for this type of venous thromboembolism (VTE). The large direct oral anticoagulants (DOAC) RCTs were performed in patients with deep vein thrombosis or pulmonary embolism and patients with SVT were not included. The question is whether DOACs can be recommended for the treatment of patients with SVT having an indication for anticoagulants. Since many patients with SVT may have comorbidities/ bleeding risk factors, including portal hypertension and oesophageal varices, that are of clinical relevance for the use of anticoagulation and particularly DOACs, the lack of (experience in) a widely available antidote, can have clinical implications and part of decision making. Here we reviewed the present literature on the use of DOACs in patients with SVT.

Search and select

A systematic review of the literature was performed to answer the following question: what are the (un)desirable effects of treatment with Direct Oral Anticoagulants (DOAC) in adult patients with acute SVT, compared to treatment with low-molecular weight heparin (LMWH), vitamin K antagonist (VKA) or heparin?

P	**(Patients)**	adult patients with acute SVT (acute portal vein thrombosis, acute Budd Chiari syndrome, acute hepatic vein thrombosis, acute splenic vein thrombosis, acute SVT, acute mesenteric vein thrombosis)
I	**(Intervention)**	DOAC
C	**(Comparison)**	LMWH, VKA, heparin
O	**(Outcomes)**	major bleeding, clinically relevant non major bleeding (CRNMB), mortality, recurrent VTE, progression of SVT, (partial) resolution of SVT, liver failure, liver transplantation, need for surgical or radiological intervention

Relevant outcome measures

The guideline development group considered major bleeding, progression of SVT, (partial) resolution of SVT and mortality as critical outcome measures for decision making; CRNMB, recurrent venous thromboembolic event (VTE), liver failure, liver transplantation and need for surgical or radiological intervention as important outcome measures for decision making.

The working group defined the outcome measures as follows:

- Major bleeding: fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin levels of 1.24 mmol/L (20 g/L or greater) or more, or leading to a transfusion of 2 U or more of whole blood or red cells, as defined by International Society of Thrombosis and Haemostasis;
- Recurrent VTE: objectively confirmed VTE, including recurrent SVT;
- Need for surgical or radiological intervention: Transjugular Intrahepatic Portosystemic Shunt (TIPS), thrombosuction, bowel resection.

A priori, the working group did not define the other outcome measures listed above but used the definitions used in the studies.

The working group defined a risk difference of 3%* as a minimal clinically (patient) important difference for major bleeding, progression of SVT, (partial) resolution of SVT, mortality, clinically relevant non major bleeding and recurrent VTE. For all other outcome measures, the default thresholds proposed by the international GRADE working group were used as a threshold for clinically relevant differences: a 25% difference in relative risk (RR) for dichotomous outcomes (RR< 0.8 or RR> 1.25), and 0.5 standard deviations (SD) for continuous outcomes.

Since presence of liver cirrhosis is an important underlying cause for SVT and factor in deciding on type of anticoagulants for the treatment of patients with SVT, subgroup analysis will be performed for patients with liver cirrhosis and patients without liver cirrhosis.

**Based on the differences applied in the guidelines on thromboprophylaxis in patients with COVID-19. This working group derived the minimal clinically (patient) important differences from the ACCP (2012).*

Search and select (Methods)

Two literature searches were performed. At first, we searched for systematic reviews and RCT and after this we performed an additional search to supplement the selected review(s) with observational studies that were published after the search date of the selected review(s).

Search 1: Systematic reviews (SR) and RCTs

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until July 5th, 2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 669 hits. Studies were selected based on the following criteria: (systematic reviews of) RCTs and observational studies which evaluated the effectiveness of DOAC in adult patients with acute SVT, compared to treatment with heparin, LMWH or VKA. 37 studies were initially selected based on title and abstract screening. After reading the full text, 36 studies were excluded (see the table with reasons for exclusion under the tab Methods), and only one study was included (Valeriani, 2021).

Search 2: Observational studies

The search strategy of the systematic review (Valeriani, 2021) was completed on December 19th, 2019. Therefore, we performed an additional search on observational studies in the databases Medline (via OVID) and Embase (via Embase.com) with relevant search terms between 1st of January 2019 until the 30th of October 2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 553 hits. Studies were selected based on following criteria: observational studies which compared the effectiveness of DOAC in adult patients with acute SVT. Following studies were excluded:

- Switch over studies in which patients that switched from (long-term) conventional anticoagulants to DOACs are considered as patients in the DOAC group.
- Studies that primarily included patients with chronic SVT.
- Studies that primarily included patients with hepatocellular carcinoma and SVT, because characteristics/treatment options/prognosis of those patients differ significantly from other patients with acute SVT.

In selection of the studies, it seemed difficult to select the studies that only included patients with an acute SVT. In the study of Khan (2022) 43% of the patients had a chronic SVT. This study was excluded. However, in other studies it was not specified whether patients with acute and/or chronic SVT were included (Nagaoki, 2018 and Zhang, 2023). The working group decided to include those studies in the literature analysis, as in clinical practice it is also often not known if an SVT is acute or of older age. It is however important to take this into account in interpreting the results.

18 studies were initially selected based on title and abstract screening. After reading the full text, 12 studies were excluded (see the table with reasons for exclusion under the tab Methods), and six studies were included.

In total, 1 SR (search 1) and six observational studies (search 2) were included.

Results

Seven studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Valeriani (2021) performed a systematic review to evaluate the effect of anticoagulation treatments in adults with splanchnic vein thrombosis. Several databases were searched up to December 2019, including Medline and Embase. They included 97 studies (N=7969), of which four studies reported data on the effect of treatment with direct oral anticoagulants (DOAC) (Hanafy, 2019; Nagaoki, 2018; Wille, 2019 and Sharma, 2020). However, only the study of Nagaoki (2018) was included in our literature analysis, since the publication of Hanafy (2019) was retracted, Sharma (2020) included also patients in the DOAC-group, when they switched from treatment with VKA to treatment with DOAC and the number of patients using DOAC was too limited in Wille (2018). Quality of the observational studies was assessed using the ROBINS-I tool.

Naymagon (2020) performed a retrospective cohort study to evaluate the efficacy and safety of DOACs in patients with non-cirrhotic acute portal vein thrombosis (PVT), compared to treatment with VKA, LMWH or no anticoagulation. They included 330 patients in a large urban tertiary center in the USA. In total, 108 patients received warfarin, 70 patients

received enoxaparin and 93 patients received DOACs. Results on the no anticoagulation group are not considered in our literature analysis. Results on the outcome bleeding events and mortality were reported for the different anticoagulation groups, which was the case for other outcome measures.

Ilcewicz (2021) performed a retrospective cohort study to evaluate the effectiveness and safety of DOACs in patients with new PVT, compared to treatment with warfarin. They included 33 patients admitted to a large academic medical center in the USA. In total, 20 patients received DOACs and 13 patients received warfarin. Patients with cirrhosis were also included (N=10). Important outcome measures were bleeding events and recurrence of thrombo-embolic events.

Kawata (2021) performed a retrospective cohort study to evaluate the management and outcomes of patients with SVT. They included 155 patients with a newly diagnosed episode of SVT at the Thrombosis Clinic in a tertiary care hospital in Canada, of which 47 received DOAC and 98 received LWMH or VKA. SVT should have been objectively documented by imaging. Patients with cirrhosis were also included. Progression of SVT, major bleeding and clinically relevant non major bleeding (CRNMB) were important outcome measures.

Naymagon (2021) performed a retrospective cohort study to share their experiences with the anticoagulation treatment of patients with PVT and liver cirrhosis. They included 214 patients with an acute PVT and cirrhosis which were seen in a tertiary care hospital in the USA and primarily focused on the comparison between patients treated with anticoagulation (DOAC (N=18), warfarin (N=26) and enoxaparin (N=42)), and patients not treated with anticoagulation. Patients not receiving any anticoagulant were not included in our analysis. They also reported outcomes by the different anticoagulants, namely major bleeding, mortality and extension of the PVT.

Naymagon (2021-B) performed a retrospective cohort study to compare anticoagulants in the treatment of patients with acute PVT and inflammatory bowel disease (IBD). They included 63 patients which were seen in a tertiary care hospital in the USA. Patients received DOAC (N=23), warfarin (N=22) or enoxaparin (N=13). Five patients did not receive any anticoagulation, but were not included in our analysis. They reported on amongst others mortality, major bleeding and need for an additional intervention.

Zhang (2023) performed a retrospective cohort study to evaluate the safety and efficacy of anticoagulants in the treatment of PVT in patients with cirrhosis. They included 77 patients who were admitted to the liver disease center of a tertiary hospital in China. Their study focused primarily on the comparison between anticoagulation (DOAC, N=18; warfarin, N=6, heparin, N=1 and nadroparin, N=2)) and no-anticoagulation (N=50). They only compared the safety of DOAC versus warfarin. Therefore only data on the outcome measure major bleeding is included in our analysis.

Table 1 lists more details on the included studies.

Author, year (design)	Participants	Characteristics of PVT	Liver cirrhosis and malignancy (%)	Intervention	Comparison	Follow-up
Nagaoki (2018), retrospective	N=50 (I: 20, C: 30) Age: I: 69 (53-74), C: 67 (24-83) Sex (M): I: 35, C: 57	PVT, not reported whether it was acute or chronic	Cirrhosis: 100 Malignancy: *HCC* I: 30; C: 63	Edoxaban* mean duration: 6 months	VKA* mean duration: 6 months	6 months
Naymagon (2020), retrospective	N=330, of which N=57 not using AC (I 93, C1 108, C2 70) Age: I: 47.1 (15.2); C1: 50.4 (14.8); C2: 51.4 (16.9) Sex (M): I: 50.5; C1: 52.8; C2: 38.6	PVT, acute	Cirrhosis: 0 Malignancy: *Non-HCC malignancy* I: 5.4; C1: 1.9; C2: 14.3	Apixaban, Dabigatran, Rivaroxaban At least for 3 months	VKA (C1), LMWH (C2), Fondaparinux**, no AC** At least for 3 months	I: 28.1 ± 11.3 months C1: 55.8 ± 27.4 months C2: 33.0 ± 18.9 months
Ilcewicz (2021), retrospective	N=33 (I:13, C: 20) Age: I: 60 ± 18; C: 51 ± 12 Sex (M) I: 69; C: 75	New PVT	Cirrhosis: *Previous diagnosis of cirrhosis* I:38; C: 25 Malignancy: NR	Apixaban, rivaroxaban mean duration: 3 months	VKA mean duration: 3 months	90 days
Kawata (2021), retrospective	N=136 (I: 43, C: 93) Age: I: 59±15; C: 55±15	New episode of SVT	Cirrhosis: 19.4 Malignancy: *Abdominal malignancy*	Apixaban, edoxaban, rivaroxaban	VKA/LMWH/no AC** mean duration: 483 (359 – 606) days	6 (3-10) months for thrombotic outcomes and 9 (4-15) months for

	Sex (M): I: 64; C: 59		31	mean duration: 483 (359 –606) days		bleeding outcomes
Naymagon (2021), retrospective	N=214, of which N=86 using AC Age:**** 60 (54–67) Sex (M): **** 60.5	Acute PVT	Cirrhosis: 100 Malignancy: *Concurrent HCC:* 15.1	Rivaroxaban, apixaban, dabigatran median duration of AC: 18.8 (10.8–52.8) months	Warfarin/ enoxaparin/no AC** median duration of AC: 18.8 (10.8–52.8) months	NR Median of 21 (11–44) months for patients using AC
Naymagon (2021_B) retrospective	N=63,of which N=58 using AC Age (median (IQR)): I: 42 (29-53); C1: 43 (33-54); C2: 44 (32-53) Sex (M): I: 73.9; C1: 46.2; C2: 63.6	Acute PVT and IBD	Cirrhosis: 6 Malignancy: NR	Rivaroxaban, apixaban, dabigatran median duration 3.9 (2.7-6.1) months	Warfarin (C1), enoxaparin (C2)/no AC** median duration of warfarin 8.5 (3.9-NA) months, for enoxaparin not reported	I: 12 (6-35) months C1: 43 (9-80) months C2: 23 (10-58) months
Zhang (2023), retrospective	N=77 of which N=27 using AC Age: 60.4 ± 12.3*** Sex (M): 67***	PVT, not reported whether it was acute or chronic	Cirrhosis: 100 Malignancy: *HCC* 7	DOAC Median duration of AC: 6 (2-11) months	Warfarin Median duration of AC: 6 (2-11) months	NR Median of 28.5 months for patients using AC

***All patients were first treated with danaparoid sodium and Anthrobin P for 3 days at 1500 units/day i.v. in those patients whose antithrombin III activity decreased by less than 70%. ** Not included in our literature analysis. ***Age and sex are not reported by AC used but only for the total group patients receiving anticoagulants. Results are reported as % (sex, cirrhosis and malignancy) or as mean ± SD/Median (IQR, age). DOAC: direct oral anticoagulants; HCC: hepatocellular carcinoma; IBD: inflammatory bowel disease; LMWH: low-molecular weight heparin; M: Male; NR: not reported; PVT: Portal vein thrombosis; VKA: vitamin K antagonist**

Results

Since part of the studies compared data on treatment with DOAC versus VKA, and on DOAC versus LMWH, it was decided to present the data on those comparisons separately.

Major bleeding

Valeriani (2021), Ilcewicz (2021), Kawata (2021), Naymagon (2021) and Zhang (2023) reported on major bleeding, which was defined as a fatal and/or symptomatic bleeding in a critical area or organ, bleeding leading to a reduction of 2 g/dl or more in hemoglobin concentration or necessitating transfusion of two or more blood units (according to ISTH criteria). Valeriani (2021) included only data of Nagaoki (2018).

Besides, Naymagon (2020) and Naymagon (2021_B) reported on major bleeding, which was however defined as GRADE 3 or 4 according to WHO criteria. We decided not to include these data in the pooled data analysis, but report them separately.

Total group

DOAC vs VKA

Nagaoki (2018), Ilcewicz (2021), Naymagon (2021) and Zhang (2023) reported on major bleeding, for the comparison DOAC versus VKA. In total for 7/69 (10.1%) patients a major bleeding was reported in the DOAC group, compared to 8/82 (9.8%) patients in the VKA group (Figure 1). This corresponds to a risk ratio (RR, 95%CI) of 1.13 (0.44 to 2.86), which is in favor of the VKA group. Corresponding risk difference (RD, 95%CI) is 0.01 (-0.09 to 0.10), which is not considered to be clinically relevant.

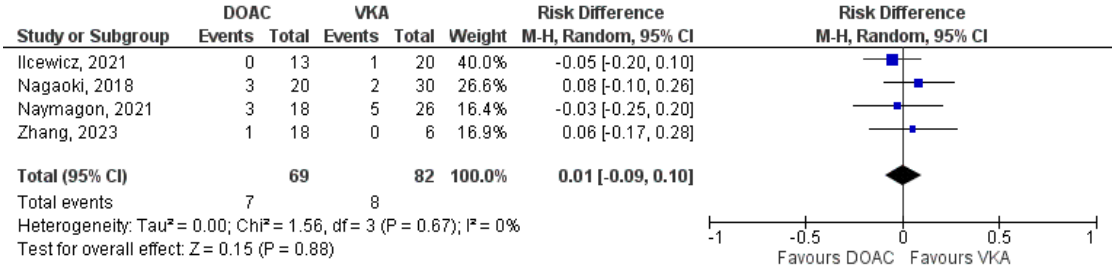


Figure 4: Forest plot for the effect of DOACs on the outcome measure major bleeding (according to ISTH criteria) in patients with acute splanchnic vein thrombosis, compared to VKA.

Naymagon (2020) and Naymagon (2021_B) reported that in respectively 2/93 (2.2%) and 0/18 (0%) of the patients in the DOAC group major bleeding was reported, compared to 26/108 (24.1) and 3/22 (13.6%) patients in the VKA group. This corresponds to RRs (95%CI) of respectively 0.09 (0.02 to 0.37) and 0.17 (0.01 to 3.14) which are in favor of the DOAC groups. Corresponding RDs (95%CI) are -0.22 (-0.31 to -0.13) and -0.20 (-0.28 to -0.13), which is considered clinically relevant.

DOAC vs LMWH

Naymagon (2021) reported on major bleeding for the comparison DOAC versus LMWH. In the DOAC group, for 3/18 (16.7%) patients major bleeding was reported, compared to 9/42 (21.4%) patients in the LMWH group. This corresponds to a RR (95%CI) of 0.78 (0.24 to 2.54) which is in favor of the DOAC group. Corresponding RD (95%CI) is -0.05 (-0.26 to 0.16), which is considered clinically relevant.

Naymagon (2020) and Naymagon (2021_B) reported that in respectively 2/93 (2.2%) and 0/18 (0%) of the patients in the DOAC group major bleeding was reported, compared to 10/70 (14.3%) and 1/13 (7.7%) patients in the LMWH group. This corresponds to RRs (95%CI)

of respectively 0.15 (0.03 to 0.67) and 0.25 (0.01 to 5.59) which are in favor of the DOAC group. Corresponding RDs (95%CI) are -0.26 (-0.37 to -0.15) and -0.08 (-0.25 to 0.10) which are considered clinically relevant.

DOAC vs LMWH/VKA

Kawata (2021) did not differentiate between patients receiving LMWH or VKA. They reported major bleeding in 3/47 (6.4%) patients in the DOAC group, compared to 6/98 (6.1%) patients in the LMWH/VKA group. This corresponds to a RR (95%CI) of 1.04 (0.27 to 3.99), which is in favor of the LMWH/VKA group. The corresponding RD (95%CI) is 0.00 (-0.08 to 0.09), which is not considered to be clinically relevant.

Patients with cirrhosis

DOAC vs VKA

Nagaoki (2018), Naymagon (2021) and Zhang (2023) reported on major bleeding in patients with cirrhosis for the comparison between DOAC versus VKA. In total, for 7/56 (12.5%) patients, major bleeding was reported in the DOAC group, compared to 7/62 (11.3%) patients in the VKA group (Figure 2). This corresponds to a RR (95%CI) of 1.22 (0.46 to 3.24) which is in favor of the VKA group. The corresponding RD (95%CI) is 0.05 (-0.07 to 0.17), which is considered clinically relevant.

Besides, Ilcewicz (2021) reported that for none of the 10 patients with a previous diagnosis of cirrhosis a bleeding event was reported.

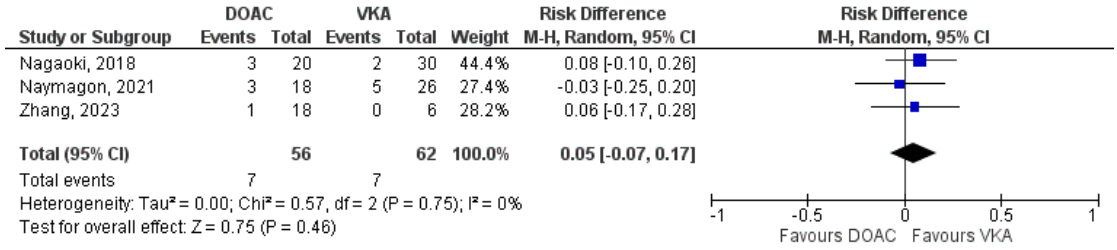


Figure 5: Forest plot for the effect of DOACs on the outcome measure major bleeding (according to ISTH criteria) in patients with acute splanchnic vein thrombosis and cirrhosis, compared to VKA.

DOAC vs LMWH

Naymagon (2021) reported on the outcome measure major bleeding in patients with cirrhosis for the comparison between DOAC versus LMWH – see also the results for the total group: in the DOAC group, for 3/18 (16.7%) patients a major bleeding was reported, compared to 9/42 (21.4%) patients in the LMWH group. This corresponds to a RR (95%CI) of 0.78 (0.24 to 2.54) which is in favor of the DOAC group. Corresponding RD (95%CI) is -0.05 (-0.26 to 0.16), which is considered clinically relevant.

Patients without cirrhosis

Naymagon (2020) reported on major bleeding in patients without cirrhosis, which was defined as GRADE 3 or 4 according to the WHO criteria. Data are reported here, but not used to draw conclusions on the effect of DOAC on the outcome measure major bleeding in patients without cirrhosis, compared to either VKA or LMWH.

DOAC vs VKA

Naymagon (2020) reported on major bleeding in patients without cirrhosis for the comparison DOAC versus VKA. For 2/93 (2.2%) of the patients in the DOAC group major bleeding was reported, compared to 26/108 (24.1%) patients in the VKA group. This corresponds to a RR (95%CI) of 0.09 (0.02 to 0.37), which is in favor of the DOAC group. Corresponding RD (95%CI) is -0.22 (-0.31 to -0.13), which is considered clinically relevant.

DOAC vs LMWH

Naymagon (2020) reported on major bleeding in patients without cirrhosis for the comparison DOAC versus LMWH. For 2/93 (2.2%) in the DOAC group major bleeding was reported, compared to 10/70 (14.3%) patients in the LMWH group. This corresponds to a RR (95%CI) of 0.15 (0.03 to 0.67) which is in favor of the DOAC group. Corresponding RD (95%CI) is -0.12 (-0.21 to -0.03), which is considered clinically relevant.

Progression of SVT

Valeriani (2021), Ilcewicz (2021), Kawata (2021) and Naymagon (2021) reported on progression of SVT which was respectively defined as progression of SVT at follow-up imaging (Valeriani, 2021), extension into previously uninvolved vessels or increase in the length/volume of the clot in the same vessel on imaging at 3, 6, and between 6 and 24 months, with a minimum observation period of 6 months (Kawata, 2021), PVT extension (Naymagon, 2021) or not defined (Ilcewicz, 2021). Valeriani (2021) included data of Nagaoki (2018).

Total group

DOAC vs VKA

Nagaoki (2018), Ilcewicz (2021) and Naymagon (2021) reported on progression SVT for the comparison DOAC vs VKA. In total, for 2/51 (3.9%) of the patients in the DOAC group was progression of SVT reported, compared to 19/76 (25%) patients in the VKA-group (Figure 4). This corresponds to a RR (95%CI) of 0.22 (0.06 to 0.82), which is in favor of the DOAC group. Corresponding RD (95%CI) is -0.18 (-0.41 to 0.05), which is considered clinically relevant.

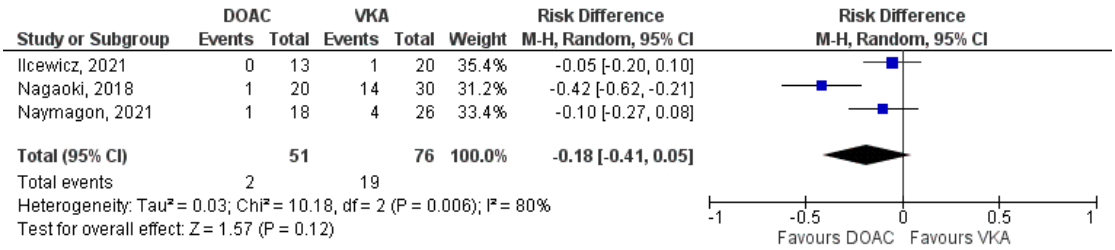


Figure 6: Forest plot for the effect of DOACs on the outcome measure progression of SVT in patients with acute splanchnic vein thrombosis, compared to VKA.

DOAC vs LMWH

Naymagon (2021) reported on progression SVT for the comparison DOAC vs LMWH. For one of the patients in the DOAC group (N=18) progression of SVT was reported, compared to 8/42 (19.0%) patients in the LMWH group. The corresponding RR (95%CI) is 0.29 (0.04 to 2.16), which is in favor of the DOAC group. The corresponding RD (95%CI) is -0.13 (-0.29 to 0.02), which is considered clinically relevant.

DOAC vs LMWH/VKA

Kawata (2021) did not differentiate between patients receiving LMWH or VKA. In total for 3/43 (7.0%) patients, progression of SVT was reported in the DOAC group, compared to 5/93 (5.4%) patients in the LMWH/VKA group. This corresponds to a RR (95%CI) of 1.16 (0.29 to 4.62), which is in favor of the LMWH/VKA group. The corresponding RD (95%CI) is 0.01 (-0.08 to 0.10), which is not considered clinically relevant.

Patients with cirrhosis

DOAC vs VKA

Nagaoki (2018), Ilcewicz (2021) and Naymagon (2021) reported on progression of SVT for the comparison DOAC versus VKA in patients with cirrhosis. As is depicted in Figure 3, RDs (95%CI) based on data of Nagaoki (2018) and Naymagon (2021) are respectively -0.42 (-0.62 to -0.21) and -0.10 (-0.27 to 0.08), which are in favor of the DOAC group and are not considered clinically relevant. Finally, Ilcewicz (2021) reported that in none of the 10 patients with previous diagnosis of cirrhosis progression of SVT was found.

DOAC vs LMWH

Naymagon (2021) reported on progression of SVT for the comparison DOAC vs LMWH in patients with cirrhosis – see also results for the total group: for one of the patients in the DOAC group (N=18) progression of SVT was reported, compared to 8/42 (19.0%) patients in the LMWH group. The corresponding RR (95%CI) is 0.29 (0.04 to 2.16), which is in favor of the DOAC group. The corresponding RD (95%CI) is -0.13 (-0.29 to 0.02), which is considered clinically relevant.

Patients without cirrhosis

None of the included studies reported on progression of SVT for patients without cirrhosis.

(partial) Resolution of SVT

Valeriani (2021), Kawata (2021), Naymagon (2020), Naymagon (2021-B), Naymagon (2021) and Zhang (2023) reported on (partial) resolution of SVT which was respectively defined as:

- any grade of recanalization (partial or complete) at follow-up imaging (Valeriani, 2021);
- either complete resolution (no evidence of thrombus in subsequent imaging) or partial resolution (objective reduction in the number of vessels involved or the length of the clot), on imaging at three, six, and between six and 24 months, with a minimum observation period of six months (Kawata, 2021);
- complete radiographic resolution of PVT established on follow-up imaging (Naymagon, 2020; Naymagon, 2021 and Naymagon, 2021_B);
- partial (> 50% reduction of the thrombus) or complete (complete disappearance of the thrombus) PVT recanalization (Zhang, 2023).

Valeriani (2021) included data of Nagaoki (2018).

Total group

DOAC vs VKA

Nagaoki (2021), Naymagon (2020), Naymagon (2021), Naymagon (2021_B) and Zhang (2023) reported on (partial) resolution of SVT for the comparison DOAC vs VKA. In total, for 111/154 (72.1%) of the patients in the DOAC-group was complete resolution of SVT reported, compared to 69/186 (37.7%) patients in the VKA-group (Figure 4). This corresponds to a RR (95%CI) of 5.18 (1.49 to 18.09), which is in favor of the DOAC-group. Corresponding RD (95%CI) is 0.35 (0.15 to 0.56), which is considered clinically relevant.

Zhang (2023) reported on partial or complete SVT recanalization. However, number of events was not reported. Therefore, these data could not be included in the pooled analysis. Hazard ratio (95%CI) was 4.05 (0.5 to 37.7), which is in favor of the DOAC-group and is considered clinically relevant.

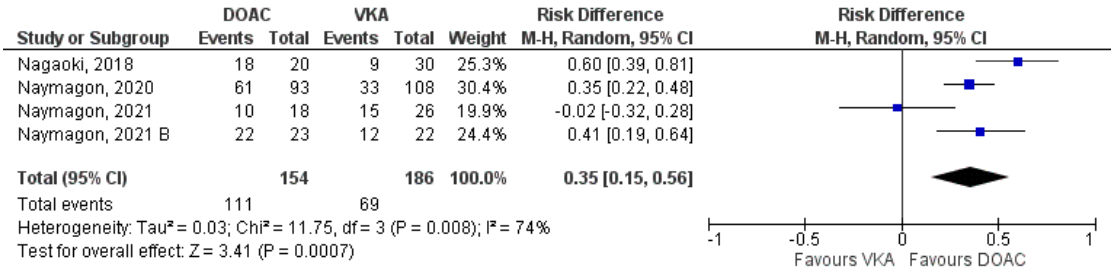


Figure 7: Forest plot for the effect of DOACs on the outcome measure (partial) resolution of SVT in patients with acute splanchnic vein thrombosis, compared to VKA.

DOAC vs LMWH

Naymagon (2020), Naymagon (2021), Naymagon (2021_B) reported on (partial) resolution of SVT for the comparison DOAC vs LMWH. In total, for 93/134 (69.4%) of the patients in the DOAC group was complete resolution of SVT reported, compared to 66/125 (52.8%) patients in the VKA-group (Figure 5). This corresponds to a RR (95%CI) of 1.21 (1.01 to 1.46), which is in favor of the DOAC-group. Corresponding RD (95%CI) is 0.12 (0.01 to 0.24), which is considered clinically relevant.

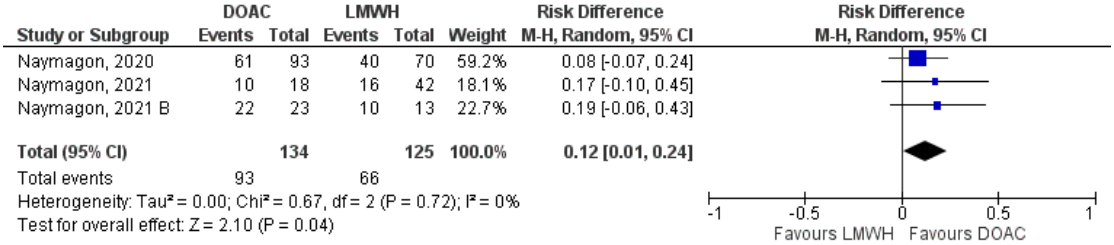


Figure 8: Forest plot for the effect of DOACs on the outcome measure (partial) resolution of SVT in patients with acute splanchnic vein thrombosis, compared to LMWH.

DOAC vs LMWH/VKA

Kawata (2021) did not differentiate between patients receiving LMWH or VKA. In total for 25/43 (58.1%) patients (partial) resolution of SVT was reported in the DOAC-group, compared to 54/83 (65.1%) patients in the LMWH/VKA-group. This corresponds to a RR (95%CI) of 0.89 (0.66 to 1.20), which is in favor of the LMWH/VKA-group. The corresponding RD (95%CI) is -0.07 (-0.25 to 0.11), which is considered clinically relevant.

Patients with cirrhosis

DOAC vs VKA

Nagaoki (2021), Naymagon (2021) and Zhang (2023) reported on (partial) resolution of SVT for the comparison DOAC vs VKA. Zhang (2023) did not report the number of events, so results could not be pooled and are reported in Table 2. Results are inconsistent, since Nagaoki (2021) and Zhang (2023) reported results in favor of the DOAC-group while Naymagon (2021) reported a non-clinically relevant difference in favor of the VKA-group.

Table 2: Results on the effect of DOACs on the outcome measure (partial) resolution of SVT in patients with acute splanchnic vein thrombosis and cirrhosis, compared to VKA.

Study	DOAC-group (n/N (%))	VKA-group (n/N (%))	Effect estimate (95%CI)
Nagaoki (2021)	18/20 (90)	9/30 (30)	RD: 0.60 (0.39 to 0.81) RR: 3.00 (1.70 to 5.28)
Naymagon (2021)	10/18 (55.6)	15/26 (57.7)	RD: -0.02 (-0.32 to 0.28) RR: 0.96 (0.57 to 1.63)

Zhang (2023)	NR	NR	HR: 4.045 (0.52 to 37.67)

RD: Risk difference, RR: risk ratio, HR: Hazard ratio, DOAC: direct oral anticoagulants, NR: not reported, VKA: vitamin K antagonists

DOAC vs LMWH

Naymagon (2021) reported on (partial) resolution of SVT for the comparison DOAC vs LMWH. For 10/18 (55.6%) patients (partial) resolution of SVT was reported in the DOAC-group, compared to 16/42 (0.4%) patients in the LMWH/VKA-group. This corresponds to a RR (95%CI) of 1.46 (0.83 to 2.57), which is in favor of the DOAC-group. The corresponding RD (95%CI) is 0.17 (-0.10 to 0.45), which is considered clinically relevant.

Patients without cirrhosis

DOAC vs VKA

Naymagon (2020) and Naymagon (2021_B) reported on (partial) resolution of SVT for the comparison DOAC vs VKA. Results are reported in Table 3. Differences are in favor of the DOAC-group and are considered clinically relevant.

Table 3: Results on the effect of DOACs on the outcome measure (partial) resolution of SVT in patients with acute splanchnic vein thrombosis without cirrhosis, compared to VKA.

Study	DOAC-group (n/N (%))	VKA-group (n/N (%))	Effect estimate (95%CI)
Naymagon (2020)	61/93 (65.6)	33/108 (30.6)	RD: 0.35 (0.22 to 0.48) RR: 2.15 (1.56 to 2.96)
Naymagon (2021_B)	22/23 (95.7)	12/22 (54.5)	RD: 0.41 (0.19 to 0.64) RR: 1.75 (1.19 to 2.59)

RD: Risk difference, RR: risk ratio, DOAC: direct oral anticoagulants, VKA: vitamin K antagonist

DOAC vs LMWH

Naymagon (2020) and Naymagon (2021_B) reported on (partial) resolution of SVT for the comparison DOAC vs LMWH. Results are reported in Table 4. Differences are in favor of the DOAC-group and are considered clinically relevant.

Table 4: Results on the effect of DOACs on the outcome measure (partial) resolution of SVT in patients with acute splanchnic vein thrombosis without cirrhosis, compared to LMWH.

Study	DOAC-group (n/N (%))	LMWH-group (n/N (%))	Effect estimate (95%CI)
Naymagon (2020)	61/93 (65.6)	40/70 (57.1)	RD: 0.08 (-0.07 to 0.24) RR: 1.15 (0.89 to 1.47)
Naymagon (2021_B)	22/23 (95.7)	10/13 (76.9)	RD: 0.19 (-0.06 to 0.43) RR: 1.24 (0.91 to 1.70)

RD: Risk difference, RR: risk ratio, DOAC: direct oral anticoagulants, LMWH: low molecular weight heparin

Mortality

Naymagon (2020), Naymagon (2021) and Naymagon (2021_B) reported on mortality, which was not further defined.

Total group

DOAC vs VKA

Naymagon (2021) reported on mortality for the comparison DOAC versus VKA. In the DOAC group, 3/18 (16.7%) of the patients died, compared to 4/26 (15.4%) in the warfarin group. This corresponds to a RR (95%CI) of 1.08 (0.28 to 4.27), which is in favor of the VKA group. The corresponding RD (95%CI) is 0.01 (-0.21 to 0.23) which is not considered clinically relevant.

DOAC vs LMWH

Naymagon (2021) reported on mortality for the comparison DOAC versus LMWH. In the DOAC group, 3/18 (16.7%) of the patients died, compared to 8/42 (19.1%) in respectively the warfarin and enoxaparin group. This corresponds to a RR (95%CI) of 0.88 (0.26 to 2.92), which is in favor of the DOAC group. The corresponding RD (95%CI) is -0.02 (-0.23 to 0.19) which is not considered clinically relevant.

Naymagon (2020) and Naymagon (2021_B) reported also on mortality, but data was very limited. Naymagon (2020) reported that 12/330 (3.6%) patients died, of which three were related to PVT (enoxaparin group: N=1/70, warfarin group: N=1/108, DOAC group: N=0/93). Naymagon (2021_B) reported that 2/58 patients died during follow-up, of which one was related to PVT (warfarin group: N=1/22, enoxaparin group: N=0/13 and DOAC group: N=0/23). Since data is too limited, it cannot be used to draw conclusions on the effect of DOAC on the outcome measure mortality in patients with SVT, compared to conventional anticoagulation.

Patients with cirrhosis

DOAC vs VKA

Naymagon (2021) reported on mortality for the comparison DOAC versus VKA in patients with cirrhosis – see also results on the total group: in the DOAC group, 3/18 (16.7%) of the patients died, compared to 4/26 (15.4%) in the warfarin group. This corresponds to a RR (95%CI) of 1.08 (0.28 to 4.27), which is in favor of the VKA group. The corresponding RD (95%CI) is 0.01 (-0.21 to 0.23) which is not considered clinically relevant.

DOAC vs LMWH

Naymagon (2021) reported on mortality for the comparison DOAC vs LMWH – see also results on the total group: in the DOAC group, 3/18 (16.7%) of the patients died, compared to 8/42 (19.1%) in respectively the warfarin and enoxaparin group. This corresponds to a RR (95%CI) of 0.88 (0.26 to 2.92), which is in favor of the DOAC group. The corresponding RD (95%CI) is -0.02 (-0.23 to 0.19) which is not considered clinically relevant.

Patients without cirrhosis

Naymagon (2020) reported on mortality in patients without cirrhosis – see also results on the total group: they reported that 12/330 (3.6%) patients died, of which three were related to PVT (enoxaparin group: N=1/70, warfarin group: N=1/108, DOAC group: N=0/93). Results are too limited to draw conclusions.

Clinically relevant non-major bleeding (CRNMB)

Kawata (2021) reported on CRNMB, which was defined according to the criteria of ISTH.

Total group – DOAC versus LMWH/VKA

Kawata (2021) reported on CRNMB for the comparison DOAC versus LMWH/VKA. In the DOAC group, for 1/47 (2%) patients a CRNMB was reported, compared to 4/98 (4%) patients in the LMWH/VKA group. This corresponds to an RR (95%CI) of 0.52 (0.06 to 4.54), which is

in favor of the DOAC group. Corresponding RD (95%CI) is -0.02 (-0.08 to 0.04). This difference is not considered clinically relevant.

Patients with cirrhosis

None of the included studies reported on CRNMB for patients with SVT and cirrhosis.

Patients without cirrhosis

None of the included studies reported on CRNMB for patients with SVT, without cirrhosis.

Recurrent VTE

Ilcewicz (2021) reported on recurrent thrombo-embolic events, which was defined as VTE of typical locations, including peripheral deep vein thrombosis and pulmonary embolism, new or worsened index PVT, and other atypical VTE. We considered data on worsening of PVT in the systematic analysis for the outcome measure progression of SVT.

Total group

DOAC vs VKA

Ilcewicz (2021) reported on recurrent thrombo-embolic events. In the DOAC group for none of the 13 patients a recurrent thrombo-embolic was reported, compared to 3/20 (15%) patients in the warfarin group. For all of them a new SVT was reported.

All comparisons

Naymagon (2020) reported that recurrence of SVT was not associated with type of anticoagulants and occurred in 9 of all included 330 patients (2.7%, patients without receiving anticoagulants were also included in this group, and effect measure was not reported). Data was too limited and was therefore not used to draw conclusions on the effect of DOAC on the outcome measure recurrent VTE in patients with SVT, compared to conventional anticoagulation.

Patients with cirrhosis

Ilcewicz (2021) reported that in none of the 10 patients with cirrhosis a recurrent VTE was found. Therefore, data is too limited to draw conclusions.

Patients without cirrhosis

Naymagon (2020) reported on recurrence of SVT in patients without cirrhosis – see also results for the total group. In short, they reported that recurrence of SVT was not associated with type of anticoagulants and occurred in 9 of all included 330 patients (2.7%, patients without receiving anticoagulants were also included in this group, and effect measure was not reported).

Liver failure and liver transplantation

None of the included studies reported on liver failure and liver transplantation.

Need for surgical or radiological intervention

Total group

None of the included studies reported on need for surgical or radiological intervention by the different anticoagulation groups. However, Naymagon (2021-B) reported that three of the patients who developed symptomatic portal hypertension (SPH) received a transjugular intrahepatic portosystemic shunt (enoxaparin-group: N=2/13, warfarin group: N=1/22, DOAC group: N=0/23). Besides, Naymagon (2020) reported that 24/104 (23%) of the patients developing chronic SPH received a TIPS. They concluded that this was not significantly

different between the groups (including also the non-anticoagulants group). Data was too limited and was therefore not used to draw conclusions on the effect of DOAC on the outcome measure need for surgical or radiological intervention in patients with SVT, compared to conventional anticoagulation.

Patients with cirrhosis
None of the included studies reported on need for surgical or radiological intervention for patients with cirrhosis.

Patients without cirrhosis
Naymagon (2020) reported on patients without cirrhosis who developed chronic SPH and received a TIPS – see also results for the total group. In short, they reported that 24/104 (23%) of the patients developing chronic SPH received a TIPS. They concluded that this was not significantly different between the groups (including also the non-anticoagulants group).

Level of evidence of the literature
General remarks
In part of the studies, it was not specified whether patients with acute and/or chronic SVT were included (Nagaoki, 2018 and Zhang, 2023).

Major bleeding
All comparisons
The evidence regarding the outcome measure major bleeding (according to ISTH criteria) came from observational studies and therefore the level of evidence started as low. The level of evidence was downgraded to very low. There was high risk of bias in the studies (e.g. events might have been missed due to retrospective design of the study, risk on indication bias, time frame differed between the groups and risk on (residual) confounding, downgraded 2 levels). Besides, the effect estimate (95%CI) crossed the thresholds for clinical relevance (serious imprecision, downgraded 2 levels).

Patients without cirrhosis
None of the included studies reported on major bleeding (according to ISTH criteria) for patients without cirrhosis.

Progression of SVT
Total group (DOAC vs LMWH)
The evidence regarding the outcome measure progression of SVT came from observational studies and therefore the level of evidence started as low. The level of evidence was downgraded to very low. There was high risk of bias in the studies (e.g. progression might have been missed since there was no routine imaging/imaging was not standardized, risk on indication bias, time frame differed between the groups and risk on (residual) confounding, downgraded 2 levels). Besides, the effect estimate (95%CI) crossed one of the thresholds for clinical relevance (serious imprecision, downgraded 1 level).

Total group (DOAC vs VKA), patients with cirrhosis (DOAC vs VKA and DOAC vs LMWH)
The evidence regarding the outcome measure progression of SVT came from observational studies and therefore the level of evidence started as low. The level of evidence was downgraded to very low. There was high risk of bias in the studies (e.g. progression might have been missed since it was not sure whether there was routine imaging, risk on indication bias, time frame differed between the groups and risk on (residual) confounding,

downgraded 2 levels). Besides, the effect estimate (95%CI) crossed the thresholds for clinical relevance (serious imprecision, downgraded 2 levels).

Patients without cirrhosis
None of the included studies reported on progression of SVT for patients without cirrhosis.

(partial) resolution of SVT
Total group (DOAC vs VKA) and patients without cirrhosis (DOAC vs VKA)
The evidence regarding the outcome measure progression of SVT came from observational studies and therefore the level of evidence started as low. The level of evidence was downgraded to very low. There was high risk of bias in the studies (e.g. (partial) resolution of SVT might have been missed since it was not sure whether there was routine imaging, risk on indication bias, time frame differed between the groups and risk on (residual) confounding, downgraded 2 levels). Besides, number of included patients was low (imprecision, downgraded 1 level).

Total group (DOAC vs LMWH)
The evidence regarding the outcome measure (partial) resolution of SVT came from observational studies and therefore the level of evidence started as low. The level of evidence was downgraded to very low. There was high risk of bias in the studies (e.g. (partial) resolution might have been missed since there was no routine imaging/imaging was not standardized, risk on indication bias, time frame differed between the groups and risk on (residual) confounding, downgraded 2 levels). Besides, the effect estimate (95%CI) crossed one of the thresholds for clinical relevance (imprecision, downgraded 1 level).

Patients with cirrhosis (DOAC vs VKA)
The evidence regarding the outcome measure (partial) resolution of SVT came from observational studies and therefore the level of evidence started as low. The level of evidence was downgraded to very low. There was high risk of bias in the studies (e.g. (partial) resolution might have been missed since there was no routine imaging/imaging was not standardized, risk on indication bias, time frame differed between the groups and risk on (residual) confounding, downgraded 2 levels). Besides, results were inconsistent (inconsistency, downgraded 1 level) and the effect estimate (95%CI) crossed the thresholds for clinical relevance (imprecision, downgraded 1 level).

Patients with cirrhosis (DOAC vs LMWH) and patients without cirrhosis (DOAC vs LMWH)
The evidence regarding the outcome measure (partial) resolution of SVT came from observational studies and therefore the level of evidence started as low. The level of evidence was downgraded to very low. There was high risk of bias in the study (e.g. (partial) resolution might have been missed since there was no routine imaging/imaging was not standardized, risk on indication bias, time frame differed between the groups and risk on (residual) confounding, downgraded 2 levels). Besides, the effect estimate (95%CI) crossed the thresholds for clinical relevance (imprecision, downgraded 2 levels).

Mortality
Total group (DOAC vs VKA and DOAC vs LMWH) and patients with cirrhosis (DOAC vs VKA and DOAC vs LMWH)
The evidence regarding the outcome measure mortality came from observational studies and therefore the level of evidence started as low. The level of evidence was downgraded to very low. There was high risk of bias in the studies (e.g. risk on indication bias, time frame differed between the groups, patients with short follow-up were excluded and risk on

(residual) confounding, downgraded 2 levels). Besides, the effect estimate (95%CI) crossed the thresholds for clinical relevance (serious imprecision, downgraded 2 levels).

Patients without cirrhosis

Data was too limited and could therefore not be used to draw conclusions on the effect of DOAC on the outcome measure recurrent mortality in patients with SVT without cirrhosis, compared to conventional anticoagulation.

Clinically relevant non major bleeding

Total group (DOAC vs VKA or LMWH)

The evidence regarding the outcome measure clinically relevant non major bleeding came from an observational study and therefore the level of evidence started as low. The level of evidence was downgraded to very low. There was high risk of bias in the studies (e.g. events might have been missed due to retrospective design of the study, risk on indication bias, time frame differed between the groups and risk on (residual) confounding, downgraded 2 levels). Besides, the effect estimate (95%CI) crossed the thresholds for clinical relevance (serious imprecision, downgraded 2 levels).

Total group (DOAC vs VKA and DOAC vs LMWH), patients with cirrhosis and patients without cirrhosis

None of the included studies reported on CRNMB for patients with or without cirrhosis, nor for the comparisons between DOAC and VKA or DOAC and LMWH for the total group.

Recurrent VTE

Total group (DOAC vs VKA)

The evidence regarding the outcome measure recurrent VTE came from an observational study and therefore the level of evidence started as low. The level of evidence was downgraded to very low. There was high risk of bias in the study (e.g. recurrent VTE's might have been missed since there was no routine imaging, risk on indication bias, time frame differed between the groups and risk on (residual) confounding, downgraded 2 levels). Besides, the number of events (and patients) was very low (serious imprecision, downgraded 2 levels).

Total group (DOAC vs LMWH) and patients with cirrhosis

None of the included studies reported on recurrent VTE for patients with cirrhosis nor for the comparison between DOAC and LMWH.

Patients without cirrhosis

Data was too limited and could therefore not be used to draw conclusions on the effect of DOAC on the outcome measure recurrent VTE in patients with SVT without cirrhosis, compared to conventional anticoagulation.

Liver failure, liver transplantation and clinically relevant non major bleeding

None of the included studies reported on liver failure and liver transplantation. Therefore, no conclusion can be drawn on the effect of DOACs on the outcome measures liver failure and liver transplantation in adults with SVT.

Need for surgical or radiological intervention

Data was too limited and could therefore not be used to draw conclusions on the effect of DOAC on need for surgical or radiological intervention in patients with SVT, compared to conventional anticoagulation.

Conclusions

General remarks

In selection of the studies, it seemed difficult to select the studies that only included patients with an acute SVT. In part of the studies, it was not specified whether patients with acute and/or chronic SVT were included (Nagaoki, 2018 and Zhang, 2023). The working group decided to include those studies in the literature analysis, as in clinical practice it is also often not known if a SVT is recent or of older age. Besides, in most of the studies patients with PVT were included and it is therefore not sure whether results are also applicable to patients with other SVT. It is important to take this into account in interpreting the results.

Major bleeding

Total group and patients with cirrhosis (all comparisons)

Very low GRADE	The evidence is very uncertain about the effect of DOACs on the outcome measure major bleeding when compared with LMWH/VKA in adult patients with SVT/in adult patients with SVT and cirrhosis. *Sources: Valeriani, 2021; Ilcewicz (2021); Naymagon (2021); Kawata (2021) and Zhang (2023)*

Patients without cirrhosis (all comparisons)

No GRADE	None of the included studies reported on the outcome measure major bleeding (according to ISTH criteria) for patients without cirrhosis. Therefore no conclusion can be drawn on the effect of DOAC on the outcome measure major bleeding in patients with SVT without cirrhosis, compared to LMWH/VKA.

Progression of SVT

Total group and patients with cirrhosis (all comparisons)

Very low GRADE	The evidence is very uncertain about the effect of DOACs on the outcome measure progression of SVT when compared with LMWH/VKA in adult patients with SVT/in adult patients with SVT and cirrhosis. *Source: Valeriani, 2021; Ilcewicz, 2021; Kawata, 2021 and Naymagon, 2021*

Patients without cirrhosis (all comparisons)

No GRADE	None of the included studies reported on the outcome measure progression of SVT for patients without cirrhosis. Therefore no conclusion can be drawn on the effect of DOAC on the outcome measure progression of SVT in patients with SVT without cirrhosis, compared to LMWH/VKA.

(Partial) Resolution of SVT

Total group and patients with cirrhosis and without cirrhosis (all comparisons)

Very low GRADE	The evidence is very uncertain about the effect of DOACs on the outcome measure (partial) resolution of SVT when compared with LMWH/VKA in adult patients with SVT. *Sources: Valeriani, 2021; Kawata, 2021; Naymagon, 2020; Naymagon, 2021, Naymagon, 2021_B and Zhang, 2023*

Mortality

Total group and patients with cirrhosis (all comparisons)

Very low GRADE	The evidence is very uncertain about the effect of DOACs on the outcome measure mortality when compared with LMWH/VKA in adult patients with SVT/in adult patients with SVT and cirrhosis. *Source: Naymagon, 2021*

Patients without cirrhosis (all comparisons)

No GRADE	Data is too limited. Therefore no conclusion can be drawn on the effect of DOAC on the outcome measure mortality in patients with SVT without cirrhosis, compared to LMWH/VKA. *Source: Naymagon (2020)*

Clinically relevant non major bleeding

Total group (DOAC vs VKA or LMWH)

Very low GRADE	The evidence is very uncertain about the effect of DOACs on the outcome measure CRNMB (according to ISTH criteria) when compared with LMWH/VKA in adult patients with SVT. *Source: Kawata,2021*

Patients with cirrhosis and patients without cirrhosis (all comparisons)

No GRADE	None of the included studies reported on the outcome measure CRNMB (according to ISTH criteria) for patients with cirrhosis and patients without cirrhosis. Therefore no conclusion can be drawn on the effect of DOAC on the outcome measure CRNMB in patients with SVT with cirrhosis and patients with SVT without cirrhosis, compared to LMWH/VKA.

Recurrent VTE

Total group (DOAC vs VKA)

Very low GRADE	The evidence is very uncertain about the effect of DOACs on the outcome measure recurrent VTE when compared with VKA in adult patients with SVT. *Source: Ilcewicz, 2021*

Total group (DOAC vs LMWH)

No GRADE	None of the included studies reported on the outcome measure recurrent VTE for patients without cirrhosis. Therefore no conclusion can be drawn on the effect of DOAC on the outcome measure recurrent VTE in patients with SVT nor on patients with SVT with cirrhosis, compared to LMWH.

Patients with cirrhosis and patients without cirrhosis (all comparisons)

No GRADE	Data is too limited. Therefore no conclusion can be drawn on the effect of DOAC on the outcome measure mortality in patients with SVT without cirrhosis, compared to LMWH/VKA. *Sources: Naymagon, 2020 and Ilcewicz, 2021*

Liver failure

No GRADE	None of the included studies reported on the outcome measure liver failure. Therefore, no conclusion can be drawn on the effect of DOACs on the outcome measure liver failure in adults with acute SVT compared to LMWH/VKA.

Liver transplantation

No GRADE	None of the included studies reported on the outcome measure liver transplantation. Therefore, no conclusion can be drawn on the effect of DOACs on the outcome measure liver transplantation in adults with SVT compared to LMWH/VKA.

Need for surgical or radiological intervention

No GRADE	Data was too limited. Therefore, no conclusion can be drawn on the effect of DOACs on the outcome measure need for surgical or radiological intervention in adults with acute SVT compared to LMWH/VKA. *Sources: Naymagon, 2020 and Naymagon, 2021_B*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Op basis van de geïncludeerde studies zijn we onzeker over het effect van direct orale anticoagulantia (DOACs) op de cruciale uitkomstmaten majeure bloeding, progressie van buikvenetrombose, (partiële) resolutie van buikvenetrombose en mortaliteit, vergeleken met conventionele antistollingsmedicatie (vitamine K antagonisten (VKA) en laagmoleculairgewicht heparine (LMWH)) in patiënten met een acute buikvenetrombose. Dit geldt voor de totale groep patiënten, alsook voor de patiënten met levercirrose en patiënten zonder levercirrose. De bewijskracht van de gevonden resultaten is erg beperkt, met name vanwege het risico op bias en imprecisie. Ook zijn we onzeker over het effect van DOACs op de belangrijke uitkomstmaten recidief veneuze trombo-embolie (VTE, inclusief buikvenetrombose) en noodzaak voor chirurgische of radiologische ingreep. Geen van de

geïncludeerde studies rapporteerde gegevens over de uitkomstmaten leverfalen en levertransplantatie. De overall bewijskracht voor deze module is dan ook zeer laag en er is duidelijk sprake van een kennislacune.

De literatuur is niet eenduidig over de toepassing van DOACs bij de diverse types buikvenetrombose. In de geïncludeerde studies zijn voornamelijk patiënten met portatrombose en in mindere mate met v. mesenterica, v. lienalis trombose en trombose van meerdere buikvenen tegelijkertijd. Patiënten met een Budd-Chiari syndroom (BCS) ontbraken in de geïncludeerde studies. Het is daarom ook niet zeker of de gevonden effecten van DOACs op de cruciale uitkomstmaten van toepassing zijn op de diverse types buikvenetrombose, en in het bijzonder bij patiënten met BCS. Ook varieerde het gebruikte type DOAC tussen de studies, waarbij de meerderheid van de patiënten een Factor Xa-remmer (FXa-remmers) kreeg en een kleine minderheid dabigatran. Helaas zijn er ook geen RCT's waarin behandeling met DOACs vergeleken worden met VKA/LMWH bij patiënten met een acute SVT. Resultaten uit een niet-vergelijkende cohortstudie waarin patiënten met non-cirrotische acute buikvenetrombose werden behandeld met een DOAC (rivaroxaban), suggereren dat behandeling met rivaroxaban een alternatief zou kunnen zijn voor de standaard antistollingsbehandeling (Ageno, 2022).

De standaardbehandeling van patiënten met een acute buikvenetrombose die een indicatie hebben voor behandeling met antistolling, is therapeutisch LMWH en voor de langere termijn meestal gevolgd door VKA met een streef International Normalized Ratio (INR) tussen 2,0 en 3,0. Hierbij wordt veelal gekozen voor LMWH en niet voor ongefractioneerde heparine (UFH), tenzij er sprake is van een contra-indicatie voor LMWH (zoals ernstige nierinsufficiëntie). Het doel van deze module was te onderzoeken of behandeling met DOACs een plaats heeft bij deze patiënten. Ondanks het feit dat we onzeker zijn over het effect van DOAC's op de cruciale uitkomstmaten, suggereren de gevonden resultaten dat DOACs, waarbij met name de FXa-remmers zijn onderzocht en in mindere mate dabigatran, in ieder geval niet meer bloedingen of meer recidief trombose gaven, maar minstens vergelijkbare bloedingsrisico's en effectiviteit hadden als LMWH of VKA. Daarnaast is het in de klinische praktijk vaak lastig of niet goed mogelijk om bij het stellen van de diagnose buikvenetrombose te weten hoe lang deze al aanwezig is, en daarmee of het om een acute of een chronische buikvenetrombose gaat. Ook is onbekend welke invloed dergelijke kennis heeft op de kansen op een bloeding of trombose en daarmee ook op de veiligheid en de effectiviteit van de behandeling.

Met de acute fase wordt het moment van diagnose bedoeld, waarin sommige patiënten klinisch worden behandeld. Het post-acute moment kenmerkt zich door belangrijk herstel van klachten en de ambulante setting waarbij orale intake geen probleem (meer) is.

Een buikvenetrombose kent meerdere mogelijke oorzaken of omstandigheden waarin deze kan ontstaan. Een bekende setting is bij een infectieuze of inflammatoire ziekte in de buikholte, zoals pancreatitis of inflammatoire darmziekten (IBD). In de studie van Naymagon (2021-B) zijn patiënten met IBD geïncludeerd. Het aantal events voor de uitkomstmaten majeure bloeding en mortaliteit was te laag om uitspraken te kunnen doen over het effect van DOACs vergeleken met conventionele antistolling. Een andere risicogroep zijn patiënten met een maligniteit, in het bijzonder patiënten met een hepatocellulair carcinoom. Zij waren wisselend vertegenwoordigd in de studies en de resultaten en aantallen zijn te beperkt om hier conclusies uit te trekken. Tenslotte is er ook een verschil in patiënten met en zonder levercirrose. Het is mogelijk dat DOACs bij patiënten met gevorderde levercirrose een ander risicoprofiel hebben. In het BAVENO-consensus document wordt aangegeven dat het daarom niet mogelijk is een aanbeveling te doen over de inzet van DOACs bij deze groep patiënten (de Franchis, 2022). In de recente ISTH-richtlijn over antistolling bij een vena porta trombose en levercirrose is de aanbeveling voor patiënten met Child-Pugh A of B

levercirrose om te behandelen met een DOAC of LMWH, eventueel gevolgd door VKA. Bij patiënten met Child-Pugh C levercirrose heeft LMWH, eventueel gevolgd door VKA, de voorkeur (Carlin, 2024). Het behandelen van patiënten met een verminderde leverfunctie en een daarbij verlengde INR, kan de behandeling met VKA bemoeilijken. Dit geldt ook voor de interpretatie van de zogenaamde MELD-score, die gebruikt wordt voor de urgentiebepaling bij patiënten op de levertransplantatie-wachtlijst. LMWH blijft dan de antistolling van voorkeur, al kent dit middel voor chronisch gebruik ook beperkingen.
Er is onvoldoende bewijs om het gebruik van DOACs bij patiënten met BSC te adviseren. Er is wel ervaring vanuit de klinische praktijk om dit in individuele gevallen voor te schrijven door voorschrijvers die ervaren zijn met de behandeling van patiënten met BSC.

In het BAVENO-consensus document worden verschillende uitspraken gedaan over het gebruik van DOACs bij patiënten met een buikvenetrombose (de Franchis, 2022). Zo geven zij aan dat er bij patiënten met een verhoogd risico op bloedingen, zoals in het geval van trombocytopenie bij splenomegalie, een individuele afweging gemaakt moet worden. Een ander bloedingsrisico is het hebben van slokdarmvarices, zoals kan ontstaan door portale hypertensie ten gevolge van buikvenetrombose. Derhalve wordt in het BAVENO-consensus document aangegeven dat het raadzaam is om patiënten te screenen op slokdarmvarices en deze te behandelen, indien mogelijk voor de start van antistolling (de Franchis, 2022).

De voordelen van parenterale - boven orale - behandeling van een buikvenetrombose zijn theoretisch, tenzij er sprake is van darmischemie. In dat geval is orale therapie niet mogelijk door het kritisch ziek zijn van de patiënt. Ook is de absorptie van orale medicatie in die setting redelijkerwijs verstoord. Het ontbreken van een streefwaarde maakt monitoring van het therapeutische effect van DOACs in deze setting onmogelijk. Het is onbekend wat het effect is van buikvenetrombose die niet gepaard gaat met fulminante darmischemie, maar wel met macro- of microscopisch oedeem van de darmwand, op de absorptie.

Kortom, realiserend dat gerandomiseerde studies ontbreken, de kwaliteit van het bewijs erg laag is en de geïncludeerde studies onvoldoende antwoord geven op de gestelde vragen, is het voorstelbaar dat er, na stabilisatie van het ziektebeeld, toch gekozen wordt voor het gebruik van een DOAC (FXa-remmer) als behandeling van een acute buikvenetrombose, tenzij er sprake is van BCS en cruciale comorbiditeit zoals Child-Pugh C levercirrose, ernstig verminderde leverfunctie, darmischemie of ernstige nierfunctiestoornissen. Bij patiënten met matige levercirrose of matig verminderde leverfunctie (Child-Pugh B), is voorzichtigheid geboden (de Franchis, 2022) en gaat de voorkeur uit naar behandeling met dabigatran of edoxaban. Van de op dit moment geregistreerde DOACs zijn dabigatran en edoxaban namelijk het minst afhankelijk van hepatische klaring. Daardoor hebben deze de voorkeur bij patiënten met mogelijk verminderde leverfunctie, zoals bij levercirrose Child-Pugh B. Bij patiënten met Child-Pugh A kunnen ook andere DOACs worden voorgeschreven. De duur van de behandeling moet op individuele basis bepaald worden. Daarbij kunnen de volgende factoren meegewogen worden: locatie van de buikvenetrombose, aanwezigheid van slokdarmvarices of andere risicofactoren voor een bloeding, aanwezigheid van persisterende risicofactoren, andere relevante comorbiditeiten en de voorkeuren van de patiënt.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>
Naast een mogelijk verschillend risico op bloedingen of recidief trombose, waar de huidige studies onvoldoende uitsluitsel over geven, is voor patiënten het verschil in gebruiks(on)gemak tussen de verschillende anticoagulantia van belang. Waar DOACs een een- of tweemaal daagse inname vereisen, is bij een behandeling met VKA een eenmaal daagse dosering voldoende. Daarnaast is het meten van de INR nodig bij behandeling met

VKA, meestal eens per twee tot zes weken, waar bij chronisch gebruik zelfmeten wordt gestimuleerd. In 2020 publiceerde het Zorginstituut Nederland het rapport 'Evaluatie van de ervaringen en kosten van antistollingszorg (van Dijk, 2020). In dit rapport komt naar voren dat DOAC-gebruikers meer vrijheid ervaren door het overbodig worden van bezoeken aan de trombosedienst. Tegelijkertijd ervaren VKA-gebruikers die zelf meten en doseren ook een grote regie over hun leven.

Het grootste nadeel van DOACs (FXa-remmer) is het ontbreken of beperkte ervaring met een adequaat en direct antidotum wat het gebruik bij een hoog bloedingsrisico of in de setting van een levertransplantatie-wachtlijst onpraktischer maakt. Daarnaast is de klaring van de DOACs grotendeels afhankelijk van de nier- en leverfunctie, wat bij deze patiëntengroep relevant kan zijn.

Het grootste nadeel van de VKA-behandeling is de potentiële ontregeling van de INR door diverse factoren, zoals infecties, koorts, interacterende medicatie maar ook stress of veranderde voeding. Indien door een onderliggende leveraandoening de INR al spontaan verlengd is, kan deze de (stabiliteit van de) behandeling met VKA bemoeilijken. Ook kan het de zogenaamde MELD-score beïnvloeden, die gebruikt wordt voor patiënten op de levertransplantatie-wachtlijst.

Naast een behandeling met tabletten is behandeling met subcutane injecties (LMWH) mogelijk, die een- of tweemaal daags geprikt moeten worden. De meeste patiënten vinden injecties meer belastend dan tabletten en niet iedere patiënt kan zichzelf die injecties toedienen. Hierdoor zijn mantelzorgers of thuiszorg voor deze behandeling noodzakelijk. Onderzoek naar voorkeuren van patiënten is schaars, maar in het algemeen wordt gevonden dat orale behandeling de voorkeur heeft boven injecties, mits deze even effectief en veilig is (Hutchinson, 2019). Het is van belang om bovenstaande afwegingen met de patient te bespreken, om zo samen tot een passende behandeling te komen.

<u>Kosten (middelenbeslag)</u>
In het rapport 'Evaluatie van de ervaringen en kosten van antistollingszorg' wordt ook aandacht gegeven aan de kosten. Hierbij was de conclusie dat de kosten voor antistollingszorg gestegen waren, met name door de hogere kosten van DOAC ten opzichte van VKA. LMWH is daarentegen bij de hoogste therapeutische dosering iets duurder dan een DOAC (Farmacotherapeutisch kompas). Tenslotte zijn de meeste DOACs inmiddels (2024) uit patent en zijn de kosten van deze medicatie daardoor ook lager geworden.

<u>Aanvaardbaarheid, haalbaarheid en implementatie</u>
Alle drie de vormen van antistolling, dus LMWH, VKA en DOAC zijn gebruikelijk en gekend in de zorg voor patiënten met trombose. De verwachting is daarom dat de aanbevelingen haalbaar zijn in de klinische praktijk.

Aanbevelingen

<u>Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies</u>
Er is geen literatuur van goede kwaliteit over de voorkeursbehandeling met antistolling bij patiënten met een acute buikvenetrombose. De behandeling met LWMH in de acute fase en vervolgens LMWH of VKA in de post-acute fase is de huidige standaard en kan nog steeds worden aanbevolen. In overleg met de patiënt kan een DOAC als alternatief worden voorgeschreven voor de post-acute fase, mits in afwezigheid van BCS en cruciale comorbiditeit zoals Child-Pugh C levercirrose, ernstig verminderde leverfunctie, darmischemie of ernstige nierfunctiestoornissen.

Met de acute fase wordt het moment van diagnose bedoeld, waarin sommige patiënten klinisch worden behandeld. Het post-acute moment kenmerkt zich door belangrijk herstel van klachten en de ambulante setting waarbij orale intake geen probleem (meer) is. Daarnaast is het belangrijk bij de start van antistollingsbehandeling, of binnen enkele weken na start, de aanwezigheid van slokdarmvarices te beoordelen en indien aanwezig te behandelen. Dit met het risico op potentieel levensbedreigende bloedingen.
Gezien het ontbreken van voldoende bewijs over de veiligheid en effectiviteit van DOACs in vergelijking met de huidige behandeling met LMWH of VKA zijn de aanbevelingen zwak geformuleerd. Deze onzekerheid maakt dat de behandeling met LMWH of VKA ook in de post-acute fase de keuze van voorkeur blijft, waarbij het niet zeker is of een DOAC een verstandig(er) alternatief is.

Behandel patiënten met een buikvenetrombose (inclusief patiënten met Budd-Chiari syndroom (BCS)) **in de acute fase** met therapeutisch gedoseerde laagmoleculairgewicht heparine (LMWH).

Overweeg patiënten met een buikvenetrombose **na de acute fase** te behandelen met een vitamine K antagonist (VKA). Behandeling met een directe orale anticoagulantia (DOAC, Factor Xa-remmer) is ook een optie.

- Overweeg behandeling met een DOAC alleen als er **geen** sprake is van BCS, Child-Pugh C levercirrose, ernstig verminderde leverfunctie, veneuze darmischemie of ernstige nierfunctiestoornissen.
- Indien gekozen wordt voor behandeling met een DOAC: kies voor een Factor Xa-remmer bij patiënten met buikvenetrombose zonder levercirrose. Bij patiënten met een buikvenetrombose én Child-Pugh B levercirrose gaat de voorkeur uit naar dabigatran of edoxaban.

Kennisvragen

- Wat zijn de (on)gunstige effecten van een behandeling met DOACs bij patiënten met acute buikvenetrombose, vergeleken met conventionele behandelingen (VKA, LMWH, of evt. heparine)?
- Wat is de optimale antistollingsbehandeling bij patiënten met het Budd-Chiari-Syndroom?
- Wat zijn waarden en voorkeuren van patiënten ten aanzien van de antistollingsbehandeling bij een acute buikvenetrombose?
- Wat is de optimale behandelduur van een acute buikvenetrombose?

Literatuur

Ageno W, Beyer Westendorf J, Contino L, Bucherini E, Sartori MT, Senzolo M, Grandone E, Santoro R, Carrier M, Delluc A, De Stefano V, Pomero F, Donadini MP, Tosetto A, Becattini C, Martinelli I, Nardo B, Bertoletti L, Di Nisio M, Lazo-Langner A, Schenone A, Riva N. Rivaroxaban for the treatment of noncirrhotic splanchnic vein thrombosis: an interventional prospective cohort study. Blood Adv. 2022 Jun 28;6(12):3569-3578. doi: 10.1182/bloodadvances.2022007397. PMID: 35439303; PMCID: PMC9631568.

Candeloro M, Valeriani E, Monreal M, Ageno W, Riva N, Lopez-Reyes R, Peris ML, Beyer Westendorf J, Schulman S, Rosa V, López-Núñez JJ, Garcia-Pagan JC, Magaz M, Senzolo M, De Gottardi A, Di Nisio M. Anticoagulant therapy for splanchnic vein thrombosis: an individual patient data meta-analysis. Blood Adv. 2022 Aug 9;6(15):4516-4523. doi: 10.1182/bloodadvances.2022007961. PMID: 35613465; PMCID: PMC9636325.

Carlin S, Cuker A, Gatt A, Gendron N, Hernández-Gea V, Meijer K, Siegal DM, Stanworth S, Lisman T, Roberts LN. Anticoagulation for stroke prevention in atrial fibrillation and treatment of venous thromboembolism and portal vein thrombosis in cirrhosis: guidance from the SSC of the ISTH. J Thromb Haemost. 2024 Sep;22(9):2653-2669. doi: 10.1016/j.jtha.2024.05.023. Epub 2024 May 31. PMID: 38823454.

Van Dijk CE, Heim N and Witteveen J. Evaluatie van de ervaringen en kosten van antistollingszorg. Zorginstituut Nederland. 2020. https://www.zorginstituutnederland.nl/publicaties/rapport/2020/10/20/evaluatie-antistollingszorg

de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol. 2022 Apr;76(4):959-974. doi: 10.1016/j.jhep.2021.12.022. Epub 2021 Dec 30. Erratum in: J Hepatol. 2022 Apr 14;: PMID: 35120736; PMCID: PMC11090185.

Hutchinson A, Rees S, Young A, Maraveyas A, Date K, Johnson MJ. Oral anticoagulation is preferable to injected, but only if it is safe and effective: An interview study of patient and carer experience of oral and injected anticoagulant therapy for cancer-associated thrombosis in the select-d trial. Palliat Med. 2019 May;33(5):510-517. doi: 10.1177/0269216318815377. Epub 2018 Nov 29. PMID: 30488789; PMCID: PMC6506899.

Ilcewicz HN, Martello JL, Piechowski K. Evaluation of the efficacy and safety of direct oral anticoagulants in the treatment of portal vein thrombosis. Eur J Gastroenterol Hepatol. 2021 Jun 1;33(6):911-916. doi: 10.1097/MEG.0000000000001958. PMID: 33079786; PMCID: PMC8371984.

Kawata E, Siew DA, Payne JG, Louzada M, Kovacs MJ, Lazo-Langner A. Splanchnic vein thrombosis: Clinical manifestations, risk factors, management, and outcomes. Thromb Res. 2021 Jun;202:90-95. doi: 10.1016/j.thromres.2021.03.018. Epub 2021 Mar 21. PMID: 33798804.

Nagaoki Y, Aikata H, Daijyo K, Teraoka Y, Shinohara F, Nakamura Y, Hatooka M, Morio K, Nakahara T, Kawaoka T, Tsuge M, Hiramatsu A, Imamura M, Kawakami Y, Ochi H, Chayama K. Efficacy and safety of edoxaban for treatment of portal vein thrombosis following danaparoid sodium in patients with liver cirrhosis. Hepatol Res. 2018 Jan;48(1):51-58. doi: 10.1111/hepr.12895. Epub 2017 Apr 27. PMID: 28342265.

Naymagon L, Tremblay D, Zubizarreta N, Moshier E, Troy K, Schiano T, Mascarenhas J. The efficacy and safety of direct oral anticoagulants in noncirrhotic portal vein thrombosis. Blood Adv. 2020 Feb 25;4(4):655-666. doi: 10.1182/bloodadvances.2019001310. PMID: 32078681; PMCID: PMC7042983.

Naymagon L, Tremblay D, Zubizarreta N, Moshier E, Mascarenhas J, Schiano T. Safety, Efficacy, and Long-Term Outcomes of Anticoagulation in Cirrhotic Portal Vein Thrombosis. Dig Dis Sci. 2021 Oct;66(10):3619-3629. doi: 10.1007/s10620-020-06695-4. Epub 2020 Nov 5. PMID: 33151401.

Naymagon L_B, Tremblay D, Zubizarreta N, Moshier E, Naymagon S, Mascarenhas J, Schiano T. The Natural History, Treatments, and Outcomes of Portal Vein Thrombosis in Patients With Inflammatory Bowel Disease. Inflamm Bowel Dis. 2021 Jan 19;27(2):215-223. doi: 10.1093/ibd/izaa053. PMID: 32185400; PMCID: PMC8427727.

Valeriani E, Di Nisio M, Riva N, Cohen O, Garcia-Pagan JC, Magaz M, Porreca E, Ageno W. Anticoagulant therapy for splanchnic vein thrombosis: a systematic review and meta-analysis. Blood. 2021 Mar 4;137(9):1233-1240. doi: 10.1182/blood.2020006827. PMID: 32911539.

Valeriani E, Di Nisio M, Riva N, Cohen O, Porreca E, Senzolo M, De Gottardi A, Magaz M, Garcia-Pagan JC, Ageno W. Anticoagulant Treatment for Splanchnic Vein Thrombosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis. Thromb Haemost. 2021 Jul;121(7):867-876. doi: 10.1055/s-0040-1722192. Epub 2021 Feb 1. PMID: 33525037.

Zhang Z, Zhao Y, Li D, Guo M, Li H, Liu R, Cui X. Safety, efficacy and prognosis of anticoagulant therapy for portal vein thrombosis in cirrhosis: a retrospective cohort study. Thromb J. 2023 Jan 30;21(1):13. doi: 10.1186/s12959-023-00454-x. PMID: 36717831; PMCID: PMC9885579.

5

Bijlagen bij module antitrombotisch beleid bij buikvenetrombose

Implementatieplan

5 Verkeerslichtanalyse

15

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijke kennisvraag
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	**Sterkte van de aanbeveling**	**Bewijskracht per uitkomstmaat**	**Verkeerslicht per (sub)aanbeveling**
Behandel patiënten met een buikvenetrombose (inclusief patiënten met Budd-Chiari syndroom (BCS)) **in de acute fase** met therapeutisch gedoseerde laagmoleculairgewicht heparine (LMWH). Overweeg patiënten met een buikvenetrombose **na de acute fase** te behandelen met een vitamine K antagonist (VKA). Behandeling met een directe orale anticoagulantia (DOAC, Factor Xa-remmer) is ook een optie. • Overweeg behandeling met een DOAC alleen als er **geen** sprake is van BCS, Child-Pugh C levercirrose, ernstig verminderde leverfunctie, veneuze darmischemie of ernstige nierfunctiestoornissen.	□ Sterk (doe/ gebruik) / **X** Zwak (overweeg)	**Overall bewijskracht** □ **H** □ **M** □ **L** **X VL** □ **NG** **Range bewijskracht van alle uitkomstmaten** □ **H** □ **M** □ **L** **X VL** **X NG** **OF** □ **voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in **X ORANJE:** gebruik tabel B □ **LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in

• Indien gekozen wordt voor behandeling met een DOAC: kies voor een Factor Xa-remmer bij patiënten met buikvenetrombose zonder levercirrose. Bij patiënten met een buikvenetrombose én Child-Pugh B levercirrose gaat de voorkeur uit naar dabigatran of edoxaban.			

Implementatietabel

Aanbeveling Behandel patiënten met een buikvenetrombose (inclusief patiënten met Budd-Chiari syndroom (BCS)) **in de acute fase** met therapeutisch gedoseerde laagmoleculairgewicht heparine (LMWH). Overweeg patiënten met een buikvenetrombose **na de acute fase** te behandelen met een vitamine K antagonist (VKA). Behandeling met een directe orale anticoagulantia (DOAC, Factor Xa-remmer) is ook een optie. • Overweeg behandeling met een DOAC alleen als er **geen** sprake is van BCS, Child-Pugh C levercirrose, ernstig verminderde leverfunctie, veneuze darmischemie of ernstige nierfunctiestoornissen. • Indien gekozen wordt voor behandeling met een DOAC: kies voor een Factor Xa-remmer bij patiënten met	Op basis van de beschikbare evidentie en ervaring uit de praktijk kon er onvoldoende richting aan de besluitvorming worden gegeven. Om die reden is er geen beschrijving van belemmeringen en kansen voor implementatie van de aanbeveling toegevoegd. Disseminatie van de kennis in deze module verloopt via de standaard route. De module wordt gepubliceerd op de Richtlijnendatabase.

	buikvenetrombose zonder levercirrose. Bij patiënten met een buikvenetrombose én Child-Pugh B levercirrose gaat de voorkeur uit naar dabigatran of edoxaban.	

5

Evidence tables

Evidence table for systematic review of RCTs and observational studies (intervention studies)

Research question: What are the (un)desirable effects of treatment with Direct Oral Anticoagulants (DOAC) in adult patients with acute abdominal vein thrombosis, compared to treatment with low-molecular weight heparine (LMWH), vitamin K antagonist (VKA) or heparin?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Valeriani, 2021 Study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of RCTs/ cohort studies. *Literature search up to December, 2019* **A**: Hanafy (2018)* **B**: Nagaoki (2018) **C**: Sharma (2020)** **D**: Wille (2019)*** *Retracted article and therefore not considered in this literature review. **Part of the patients switched from VKA to DOACs and were considered in the DOAC-group. Study is excluded. ***Data on DOACs is to limited and	Inclusion criteria SR: diagnosis of SVT; observational study or RCT including ≥10 patients; availability of radiological or clinical outcomes; and anticoagulant treatment with LMWH, unfractionated heparin, fondaparinux, VKAs, DOACs or no anticoagulant therapy. Exclusion criteria SR: study design different from those specified in the inclusion criteria; inclusion	Describe intervention: **B**: Edoxaban (60 mg once daily for 6 months, dosage was halved in patients with eGFR 30-50 ml/min, patients <60 kg and patients with concurrent treatment with a strong P-glycoprotein inhibitor) **C**: Dabigatran (duration of therapy: 14.1 ± 6.9 months)	Describe control: **B**: Warfarin (dosage adjusted to achieve INR 1.5-2.0) **C**: vitamin K antagonists (duration of therapy: 10.5 ± 6.7 months)	<u>End-point of follow-up</u>: **B**: 6 months (regular clinical FU at 2 wks, 1 month, 3 months and 6 months) **C**: NR (once a month for the initial 3 months followed by once in 3 months) <u>For how many participants were no complete outcome data available?</u> **B**: NR **C**: NR	<u>Outcome major bleeding</u> Defined as major bleeding by study authors or interpreted as major by the review authors. DOAC (n/N) **B**: 3/20 **C**: 1/36 VKA (n/N) **B**: 2/30 **C**: 3/62 <u>Outcome mortality</u> Defined as overall mortality DOAC (n/N) **B**: NR **C**: 1/36 VKA (n/N) **B**: NR **C**: 3/62 LMWH (n/N) **B**: NA	<u>Risk of bias (high, some concerns or low):</u> Tool used by authors: ROBINS-I **B**: high **C**: high <u>Author's conclusion</u> In summary, anticoagulant therapy for SVT is associated with vein recanalization and low probability of thrombosis progression. The risks of recurrent VTE and major bleeding in patients receiving anticoagulation therapy and the proportion of events in those left untreated strongly suggest the need for additional studies to optimize SVT management.

	therefore this study is not considered in this literature review. <u>Study design</u>: Retrospective studies <u>Setting and Country</u>: **B**: University hospital, Japan **C**: Tertiary centre, India <u>Source of funding and conflicts of interest:</u> **B**: No funding declared, no COI **C**: None Systematic review was not funded. However, publication costs of article were defrayed in part by page charge payment.	of < 10 patients; and anticoagulant therapy different from those specified in the inclusion criteria. *97 studies included of which 4 studies on DOACs.* <u>Important patient characteristics at baseline</u>:* <u>N</u> **B**: I: 20, C: 30) **C**: I: 36, C:62 <u>*Age*</u> **B**: I: 69 (53-74) C: 67 (24-83) **C**: I:29.5 (22–35) C: 28 (23–37) <u>*Sex (male)*</u>*:* **B**: I: 65%, C: 57% **C**: I: 53%, C: 61% <u>*Child-Pugh score (mean or %)*</u> **B**: A/B/C I: 15/5/0, C: 15/10/5 **C**: I: 7 (6-8), C: 6 (5.7-7) <u>*MELD score*</u> **B**: NR				**C**: NA <u>Outcome progressive SVT</u> Defined as progression of SVT at follow-up imaging. DOAC (n/N) **B**: 1/20 **C**: NR VKA (n/N) **B**: 14/30 **C**: NR LMWH (n/N) **B**: NR **C**: NA <u>(recurrent) VTE</u> Defined as deep vein thrombosis of the lower or upper extremities, pulmonary embolism, or recurrent SVT DOAC (n/N) **B**: NR **C**: 4/36 VKA (n/N) **B**: NR **C**: 4/62 LMWH (n/N) **B**: NA **C**: NA <u>Recanalization of SVT</u> Defined as any grade of recanalization (partial or complete) at follow-up imaging	<u>Remarks</u> Sharma (2020): Any patient who was switched over to dabigatran from VKAs was considered in dabigatran arm.

		C: I: 10.8 (8.6-13), C: 11.7 (9.2-13.8) *<u>INR</u>* **B**: NR **C**: I: 1.3 (1.2-1.4), C: 1.4 (1.2-1.6) *<u>Etiology (%)</u>* *HBV/HCV/NBNC: I: 4/6/10, C: 7/16/7* **Extracted from individual studies.* Groups comparable at baseline?				**DOAC** B: 18/20 **VKA** B: 9/30	

Evidence table for intervention studies (randomized controlled trials and non-randomized *observational* studies [cohort studies, case-control studies, case series])

5 **Research question:** What are the (un)desirable effects of treatment with Direct Oral Anticoagulants (DOAC) in adult patients with acute abdominal vein thrombosis, compared to treatment with low-molecular weight heparin (LMWH), vitamin K antagonist (VKA) or heparin?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Naymagon, 2020	Type of study: Retrospective study Setting and country: Urban tertiary care center, USA	<u>Inclusion criteria</u>: Patients with ICD code for non-cirrhotic (acute) PVT seen between January 2000 and February 2019. <u>Exclusion criteria</u>: Splanchnic vein thrombosis	DOAC At least for 3 months	Control 1: Warfarin Control 2: Enoxaparin At least for 3 months	<u>Length of follow-up (mean number of months)</u>: Intervention: 28.1±11.3 Control1: 55.8±27.4 Control2: 33.0±18.9 <u>Loss-to-follow-up</u>: NR	**Major bleeding** Defined as grade 3 or 4 bleeding, WHO. Intervention: 2/93 Control1: 26/108 Control2: 10/70 Effect measure (95%CI) I vs C1: 0.20 (0.05-0.86) P=.0307;	**Authors conclusion** This study should help establish the role of DOACs in the treatment of ncPVT. Given that more than half of the patients in this cohort had concurrent thrombosis of at least 1 other splanchnic vessel,

	Funding and conflicts of interest: Non commercial funding and no COI.	without portal vein involvement, had cirrhosis or tumor thrombus, received interventional thrombolysis/thrombectomy, lacked baseline imaging of PVT at diagnosis, lacked subsequent follow-up imaging at least 3 months after diagnosis, or seemed to have chronic rather than acute PVT (eg, had known prior history of PVT or had evidence of cavernous transformation or other radiographic features to suggest chronic PVT at the time of initial diagnosis). N total at baseline: 330 of which 57 did not receive anticoagulation Intervention: 93 Control1: 108 Control 2: 70 Important prognostic factors[2]: *age (median (IQR)):* I: 47.1 (15.2) C1: 50.4 (14.8) C2: 51.4 (16.9) *Sex (M/F (%)):* I: 50.5/49.5 C1: 52.8/47.2 C2: 38.6/61.4 *Etiology* *IBD (%)* I: 6.5 C1: 5.6			Incomplete outcome data: NR	**Mortality*** Twelve patients (3.6%) died during follow-up. Three of these deaths were related to PVT (one on enoxaparin, one no AC and one warfarin). *Study excluded patients < 3 months follow-up, and thus patients who may have died of acute complications of their initial PVT would not have been included. **Recurrence of SVT** Recurrence of SVT was rare in this cohort, occurring in only 9/330 (2.7%) of patients. (not associated with type of AC). **Need for intervention** 23% who developed chronic portal hypertensive symptoms received a TIPS. Frequency did not differ significantly among groups. **Complete radiographic resolution (CRR)** Defined as complete radiographic resolution of PVT established on follow-up imaging	our conclusions can likely be generalized to all ncSVT. These findings further the ongoing trend toward expanding the indications for DOACs across subtypes of venous thromboembolism, most recently exemplified by evidence favoring their use in cancer associated thrombosis, cerebral venous thrombosis, and among morbidly obese patients.Long-term outcomes among patients with ncPVT remain somewhat disappointing, and future studies should investigate the role of early thrombolysis and/or thrombectomy (in addition to AC), particularly among those patient groups most recalcitrant to AC alone (those with JAK2V617F, those with no evident predisposing factor for PVT, and those with occlusive thrombus at diagnosis). **Remarks** - Duration of follow-up differed significantly between the groups. - Mean year of diagnosis of patients in the DOAC group was 2017 compared

		C2: 4.3 *IBD + surgery* I: 14 C1: 12 C2: 7.1 *Intraabdominal infection (%)* I: 5.4 C1: 8.3 C2: 7.1 *JAK2V617 mutation (%)* I: 7.5 C1: 13.9 C2: 7.1 *Non-HCC malignancy (%)* I: 5.4 C1: 1.9 C2: 14.3 *Pancreatitis (%)* I: 5.4 C1: 3.7 C2: 2.9 *Pregnancy (%)* I: 2.2 C1: 0 C2: 2.9 *Multiple (%)* I: 9.7 C1: 5.6 C2: 27.1 *OCP use (%)* I: 6.5 C1: 1.9 C2: 5.7				I:61/93 C1: 33/108 C2: 40/70 P=NR	to 2013 and 2015 in the control groups. - In many cases intravenous heparin was used as initial short-term (or bridging) AC, and in these instances, the first long-term AC transitioned to thereafter was considered. - 4% had a change in anticoagulation during follow-up, though only 2 of these changes occurred in the first 3 months of therapy and only 8 in the first year (but ITT analysis). - All patients completed at least 3 months of AC. 44% discontinued AC during follow-up, with the most common reasons for discontinuation being resolution of PVT and bleeding. - Patients with follow-up <3 months were excluded. - Study primarily focused on the comparison between anticoagulation and non-anticoagulation. - No information on assessment of

		Other (%) I:1.1 C1: 2.8 C2: 2.9 *PV occlusion (%)* *Occlusive* I: 57 Cl1: 63 Cl2: 51.4 *Nonocclusive* I: 43 Cl1: 37 Cl2: 48.6 *Meld-score, Child-pugh score, INR:* NR Groups comparable at baseline? No					exposure, confounding factors (but radiology reports). - Imaging during follow-up (yearly) was not significantly different between the groups.
Ilcewicz (2021)	Type of study: Retrospective cohort study Setting and country: Single academic center, USA Funding and conflicts of interest:	Inclusion criteria: Adults, admitted to academic medical center, from 2014 to 2018, initiated DOAC or warfarin for the treatment of a new PVT based on radiographic imaging. Exclusion criteria: Receiving full-dose anticoagulation for any indication other than PVT, active hepatocarcinoma, and pregnancy. N total at baseline: 33 Intervention: 13 Control: 20	DOAC for three months *Dosing* Rivaroxaban 20 mg daily, N=5 (38%) Rivaroxaban 15 mg daily, N=1 (8%) Apixaban 2.5 mg BID, N=3 (23%) Apixaban 5 mg BID, N=4 (31%)	Warfarin for three months	Length of follow-up: 90 days Loss-to-follow-up: NR Incomplete outcome data: NR	**Recurrent thrombo-embolic events** *Defined as VTE of typical locations, including peripheral deep vein thrombosis (DVT) and pulmonary embolism, new or worsened index PVT, and other atypical VTE* I: 0 C: 4 (of which one worsening of index PVT, and 3 experienced new SVT) **Bleeding events** *Severity was determined according to ISTH*	**Authors conclusion** DOACs appear to be effective and safe in the treatment of PVT and prevention of worsening and recurrent VTE. Future studies with larger sample sizes are warranted to confirm DOACs' efficacy and safety in the treatment of PVT, particularly in regard to optimal DOAC dosing regimens as well as in patients with Child-Pugh B and C cirrhosis. **Remarks** - Groups differed significantly with

		Important prognostic factors[2]: *Age (mean ± SD):* I: 60 ± 18 C: 51 ± 12 *Sex (M/F (%))* I: 69/31 C: 75/25 *Admitting diagnosis* *Pancreatitis (%)* I: 15 C: 20 *GI-bleed (%)* I: 8 C: 0 *Abdominal pain (%)* I: 46 C: 70 *Cholecystitis (%)* I: 23 C: 5 *Cirrhosis (%)* I: 38 C: 25 *INR:* I: 1.15 ± 0.6 C: 1.1 ± 0.2 *Meld-score, PV occlusion and Child-pugh score:* NR Groups comparable at baseline?				I: 0 C: 1 (which fulfilled criteria of major bleeding) Effect measure (95%CI): NR P= NR Of the 10 patients with previous diagnoses of cirrhosis, five patients received a DOAC, and the other five received warfarin. No patients with previous diagnoses of cirrhosis experienced a recurrent thrombo-embolic event or bleeding.	regard to concomitant medications (e.g. antiplatelet, beta-blocker, PPI and NSAID), which were, but NSAIDS, more frequently used in DOAC group. - 4 patients using DOACs were sub optimally dosed. - Routine re-imaging was no inclusion criterium. -

		No					
Kawata (2021)	Type of study: Retrospective study Setting and country: Single center, tertiary care, Canada Funding and conflicts of interest: funding not reported, no COI	Inclusion criteria: Adults with newly diagnosed episode of SVT evaluated at the Thrombosis Clinic between 2007 and 2018. SVT was defined as any objectively documented thrombosis by imaging such as ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI), including portal, superior/inferior mesenteric, hepatic, and/or splenic veins, or Budd Chiari syndrome Exclusion criteria: NR N total at baseline: 155 Intervention: NR Control: NR Important prognostic factors[2]: *Sex (M/F):* *I 64/36:* *C: 59/41* *Age (years±SD):* *I: 59±15* *C: 55±15* *Any local risk factors (%)* *I 74:* *C: 83* *Local risk factors (%)*	DOAC	LMWH or VKA	Length of follow-up (median (IQR)): 9 (4-16) months Loss-to-follow-up: NR Incomplete outcome data: Total: N=22 for SVT status/progression	**SVT progression (n/N (%))** Defined as extension into previously uninvolved vessels or increase in the length/volume of the clot in the same vessel. I: 3/43 (7) C: 5/83 (6) Effect measure (95%CI): P= NR **Major bleeding (n/N (%))** Defined according to criteria of ISTH. I: 3/47 (6) C: 6/98 (6) Effect measure (95%CI): P>0.9999 **Clinically relevant non-major bleeding (n/N (%))** Defined according to criteria of ISTH. I: 1/47 (2) C: 4/98 (4) Effect measure (95%CI):NR P>0.9999 **SVT status** *Complete/partial resolution* Defined as no evidence of thrombus in subsequent imaging) or objective reduction in the number of vessels involved or the length of the clot. I: 25/43 (58)	**Authors conclusion** In conclusion, our study results suggest that in SVT patient anticoagulation results in partial or complete thrombosis resolution in a significant proportion of patients with an acceptable bleeding risk and that outcomes are similar between patients with or without local risk factors. **Remarks** Two patients received more than one DOAC.

		NR for separate groups, only for total group. *<u>Malignancy:</u> 31* *<u>Cirrhosis</u>: 19.4* *<u>Abdominal infection:</u> 12.9* *<u>IBD:</u> 3.9* *<u>Abdominal surgery:</u> 20.6* *<u>Liver transplantation:</u> 5.2* *<u>Splenectomy:</u> 4.5* *<u>Abdominal trauma:</u> 1.3* *<u>Pancreatitis:</u> 11* *<u>Cholecystitis:</u> 5.2* *<u>Appendicitis:</u> 2* Groups comparable at baseline? NR				C: 54/83 (65) P = 0.446	
Naymagon (2021)	Type of study: Retrospective study Setting and country: Single center, tertiary care, USA Funding and conflicts of interest: Non-commercial funding, no COI	<u>Inclusion criteria</u>: Patients with ICD code for PVT and cirrhosis, seen between 2000 and 2019. <u>Exclusion criteria</u>: Splanchnic vein thrombosis without portal vein involvement, did not have cirrhosis, tumor thrombus, received interventional thrombolysis/ thrombectomy, lack of baseline imaging of PVT at diagnosis, lack of subsequent follow-up imaging at least 3 months following diagnosis, or seem to be chronic rather than acute PVT (e.g., had known prior history of PVT or had evidence of cavernous transformation or other radiographic features to suggest chronic PVT at the	DOAC *Dosing* Rivaroxaban 20 mg daily (following a 21 day loading period of 15 mg twice daily), Apixaban 5 mg twice daily (following a 7 day loading period of 10 mg twice daily), and Dabigatran 150 mg twice daily.	Control 1: Warfarin Control 2: enoxaparin *Dosing* Warfarin titrated to INR of 2–3 Enoxaparin 1 mg/kg twice daily	<u>Length of follow-up (median, IQR)</u> 21 (11–44) – total group AC <u>Loss-to-follow-up</u>: Patients were followed from time of diagnosis until the end of the study period, or until they were lost to follow up within the health system <u>Incomplete outcome data</u>: NR	**Major bleeding (n/N (%))** Defined according to criteria of ISTH. I: 3/18 (16.7) C: 5/26 (19.2) C2: 9/42 (21.4) Effect measure (95%CI):NR P=NR **PVT extension (n/N (%))** *Not defined* I: 1/18 (5.6) C1: 4/26 (15.4) C2: 8/42 (19.1) Effect measure (95%CI):NR P=NR **Mortality (n/N (%))** I: 3/18 (16.7) C1: 4/26 (15.4) C2: 8/42 (19.1)	**Authors conclusion** AC appeared safe in this large cohort of patients with cirrhotic PVT and was associated with higher rates of CRR and RCO, albeit without a significant improvement in OS. More data are needed to clarify whether AC may be associated with improvement in clinical outcomes such as decompensation of cirrhosis, eventual liver transplantation, and mortality. Prospective clinical trials will be needed to effectively evaluate such outcomes. **Remarks** - Study primarily focused on the

		time of initial diagnosis), proceeded to orthotropic liver transplantation within 3 months of PVT diagnosis, or without interval re-imaging prior to surgery. N total at baseline: 86 Intervention: 18 Control 1: 26 Control 2: 42 Important prognostic factors[2]: *NR for separate groups, only for total group of 86 patients.* *Sex (M/F (%)): 60.5/39.5* *Age (median, IQR): 60 (54–67)* *Concurrent HCC (%):* 15.1% *MELD (median, IQR): 10 (7-13)* *Child-Pugh (%): A: 24.4, B: 48.8, C: 26.7* *INR (median, IQR): 1.3 (1.2-1.4)* *Degree of PV occlusion (%):* *Occlusive 29.9:* *Non-occlusive: 70.1* Groups comparable at baseline? NR				Effect measure (95%CI): NR P=NR **Complete radiographic resolution (CRR)** Defined as CRR established at follow-up imaging I: 10/18 (56) C1: 15/26 (58) C2: 16/42 (38) P=NR	- comparison between anticoagulation and non-anticoagulation. - Patients were included in the treatment group if they started AC within 4 weeks of diagnosis. Discontinuation of AC was addressed via an intent-to-treat-style analysis, wherein patients were maintained in the AC group
Naymagon (2021_IBD)	Type of study: Retrospective study Setting and country:	Inclusion criteria: Patients with an ICD code for PVT seen between 2000 – 2019, concurrent history of IBD, medical records confirmed a history of acute PVT, with or without concurrent	DOAC	Control1: Warfarin Control2: Enoxaparin	Length of follow-up: I: 12 (6-35) C1: 43 (9-80) C2: 23 (10-58) Loss-to-follow-up: NR	**Major bleeding** *Defined as WHO grade 3 or 4* I: 0/18 C1: 3/22 C2: 1/13 **Mortality**	**Authors conclusion** This study demonstrates that the use of AC may potentially lead to excellent outcomes in IBD-associated PVT. Administered DOACs were associated with particularly

	Single center, tertiary care, USA Funding and conflicts of interest: No funding, no COI	thrombosis in additional splanchnic vessels. <u>Exclusion criteria</u>: Tumor thrombus, receipt of thrombolysis/ thrombectomy, absence of baseline imaging at PVT diagnosis, absence of subsequent follow-up imaging 3 or more months after diagnosis, and evidence of chronic as opposed to acute PVT at diagnosis (eg, known clinical history of long-standing PVT, or presence of portal cavernoma, portal collaterals, or other radiographic findings suggestive of chronic PVT at diagnosis). <u>N total at baseline</u>: 58 Intervention: 23 Control1:22 Control2:13 <u>Important prognostic factors</u>[2]: *Age (median (IQR)):* *I: 42 (29-53)* *C1: 43 (33-54)* *C2: 44 (32-53)* *Sex (M/F (%)):* *I: 73.9/26.1* *C1: 46.2/53.8* *C2: 63.6/36.4* *Type of IBD (%)* *<u>UC</u>* *I: 65.2*			<u>Incomplete outcome data</u>: NR	Two patients died during follow-up, with 1 death a direct complication of PVT (this person was treated with warfarin). **Need for intervention** One of the 3 patients (N=2 on enoxaparin and N=1 on warfarin), who developed SPH went on to receive a transjugular intrahepatic portosystemic shunt with subsequent improvement in portal hypertensive symptoms **Complete radiographic resolution (CRR)** Definition not reported I: 22/23 (96) C1: 12/22 (55) C2: 10/13 (77) P=NR	favorable outcomes among such patients in this retrospective study and were in particular associated with favorable efficacy and safety profiles relative to warfarin. Rates of recurrent VTE were low, and such patients may likely discontinue AC following at least 3 months of treatment, assuming that follow-up imaging shows resolution of PVT. The incidence of clinically meaningful results in thrombophilia testing was low, and such testing need not be routinely sent among this patient population. Further studies, both prospective and retrospective, would be helpful to confirm these findings. **Remarks** • Study primarily focused on the comparison between anticoagulation and non-anticoagulation. • The initial long-term AC used in each instance was recorded and formed the basis for comparison across patients. • In many patients intravenous heparin

		C1: 54.5 *C2: 69.2* *<u>CD</u>* *I: 34.8* *C1: 45.5* *C2: 30.8* *Degree of PVT occlusion* *<u>Occlusive</u>* *I: 30.4* *C1: 36.4* *C2: 38.5* *<u>Nonocclusive</u>* *I: 69.6* *C1: 63.6* *C2: 61.5* *Meld-score, Child-pugh score, INR:* *NR* Groups comparable at baseline? No					was used as initial shortterm (or bridging) AC, and in these instances the first long-term. AC transitioned to thereafter was considered.
Zhang (2023)	Type of study: Retrospective study Setting and country: Single center, liver disease center, China Funding and conflicts of interest: No funding, no COI	<u>Inclusion criteria</u>: (28) age ≥ 18 years; (2) liver cirrhosis was diagnosed according to the criteria of the JSGE and (3) PVT was diagnosed by abdominal Doppler ultrasound, MRI and CT. <u>Exclusion criteria</u>: 1)malignant related PVT; (2) isolate splenic or mesenteric venous thrombosis; (3) those receiving non-anticoagulant treatment such TIPS, antithrombotic, thrombolysis, or	DOAC *Dosing* rivaroxaban 20 mg qd (n = 3), rivaroxaban 10 mg qd (n = 14), edoxaban 30 mg qd (n = 1).	Warfarin *Dosing* *INR target level of 1.5–2.5*	<u>Length of follow-up (median)</u>: 28.5 months – total group anticoagulants <u>Loss-to-follow-up</u>: In case of loss to follow-up, patients were followed until the last record within our health system. <u>Incomplete outcome data</u>: NR	**Major bleeding** *According to the criteria of the ISTH* *I: 1/18* *C: 0/6* *Effect measure (95%CI): NR* *P= 1.000* **PVT recanalization** Defined as both complete and partial recanalization. Complete recanalization referred to the complete disappearance of the thrombus and partial recanalization to more	**Authors conclusion** In conclusion, anticoagulant therapy could increase the rate of PVT recanalization without increasing the rate of bleeding in patients with liver cirrhosis and could reduce the rate of variceal bleeding. Compared with the non-anticoagulant group, anticoagulant therapy may be beneficial to the liver function of patients with cirrhotic PVT. There was no significant difference in the safety and

		thrombectomy during liver transplantation; (4) platelet count < 10 × 109/L; (5) creatinine clearance ≤30 mL/min; (6) primary thrombophilia; (7) Budd-Chiari syndrome; (8) pregnancy or breast-feeding women; (9) severe cardiopulmonary diseases; (10) cases without imaging followup information N total at baseline: 77 of which 27 were using anticoagulants. Only 24 patients were included in the analysis (DOAC vs warfarin). Intervention: 18 Control: 6 Important prognostic factors[2]: *NR for separate groups, only for total group of 27 patients* *Age (mean±SD): 60.4 ± 12.3* *Sex (M/F (%)): 67* *Meld-score (mean±SD): 5.2 ± 4.0* *Etiology (%)* *HBV: 37* *PBC: 11* *Alcohol 26:* *NASH: 7* *Drug: 4* *Other: 15*				than 50% reduction of the thrombus I: NR C: NR HR (95%CI): 4.045 (0.52-37.67)	efficacy of different anticoagulants in the treatment of cirrhotic PVT. Further studies are needed to optimize the use of anticoagulants in patients with cirrhotic PVT. **Remarks** - Median duration of anticoagulant therapy was 6 (IQR 2–11) months. - Study primarily focused on the comparison between anticoagulation and non-anticoagulation. - Patients were followed until death, liver transplantation, or the end of the study. - MRI or CT was performed every 6 months

		Malignancies (HCC): 7 *PV-occlusion (%)* *<u>Occlusive:</u> 4* *<u>Non-occlusive</u>: 96* *INR (mean±SD): 1.2 ± 0.1* *Child-pugh score: NR* Groups comparable at baseline? NR					

Risk of bias table for interventions studies (cohort studies based on risk of bias tool by the CLARITY Group at McMaster University)

Author, year	Selection of participants Was selection of exposed and non-exposed cohorts drawn from the same population?	Exposure Can we be confident in the assessment of exposure?	Outcome of interest Can we be confident that the outcome of interest was not present at start of study?	Confounding-assessment Can we be confident in the assessment of confounding factors?	Confounding-analysis Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables?	Assessment of outcome Can we be confident in the assessment of outcome?	Follow up Was the follow up of cohorts adequate? In particular, was outcome data complete or imputed?	Co-interventions Were co-interventions similar between groups?	Overall Risk of bias

Naymagon (2020)	**Probably no** Reason: Time frame was different between the groups and there might have been indication bias. Patients with short follow-up were excluded, thus patients who may have died of acute complication of PVT were not included.	**Probably yes** Reason: No information (initial long-term AC used in each instance was recorded), but it is most likely that exposure is determined correctly.	**Definitely yes** Reason: mortality was logically not present at the start of the study, for the outcome measure major bleeding it is also not likely.	**Probably yes** Reason: radiological reports were used; for other confounders it is not sure how they were assessed.	**Definitely no** Reason: analysis was adjusted for confounding, but high risk on residual confounding	**Probably no** Reason: due to the retrospective nature of the study, it is possible that bleeding events were missed.	**Probably no** Reason: Follow-up period differed significantly between the groups. Loss to follow-up is not reported.	**No information**	**High (all outcomes)**
Ilcewicz (2021)	**Probably no** Reason: Time frame might be different between the groups, there might have been indication bias.	**Probably yes** Reason: No information, but it is most likely that exposure is determined correctly.	**Definitely yes** Reason: recurrent thrombo-embolic event was logically not present at the start of the study, for the outcome measure major	**No information**	**Definitely no** Reason: no adjustment for confounding	**Probably no** Reason: due to retrospective nature of the study, it is possible that bleeding events were missed. Besides, there	**Probably no** Reason: follow-up time might be short, especially for the outcome measure PVT recurrence. Loss to follow-	**Probably no** Reason: Groups differed significantly with regard to concomitant medications (e.g. antiplatelet, beta-blocker, PPI and NSAID),	**High (all outcomes)**

			bleeding it is also not likely.			was no routine imaging and therefore worsening or recurrence of PVT might have been underestimated.	up is not reported.	which were, but NSAIDS, more frequently used in DOAC group.	
Kawata (2021)	**Probably no** Reason: Time frame might be different between the groups, there might have been indication bias.	**Probably yes** Reason: No information, but it is most likely that exposure is determined correctly (i.e. initial anticoagulant therapy).	**Definitely yes** Reason: progression of SVT was logically not present at the start of the study, for the outcome measure bleeding it is also not likely.	**Probably yes** Reason: imaging reports were used; for other confounders it is not sure how they were assessed.	**Definitely no** Reason: no adjustment for confounding	**Probably no** Reason: Due to retrospective nature of the study, it is possible that bleeding events were missed.	**No information** Reason: Follow-up period was not reported by anticoagulant group. Loss to follow-up is not reported. Imaging was performed at 3, 6, and between 6 and 24 months, with a minimum observation period of 6 months. Result at the last	**No information**	**High (all outcomes**

							assessment was reported.		
Naymagon (2021)	**Probably no** Reason: Time frame might be different between the groups, there might have been indication bias. Patients with short follow-up (imaging < 3 months) were excluded, thus patients who may have died of acute complication of PVT were not included.	**Probably yes** Reason: No information (initial long-term AC used in each instance was recorded), but it is most likely that exposure is determined correctly.	**Definitely yes** Reason: PVT extension and mortality was logically not present at the start of the study, for the outcome measure major bleeding it is also not likely.	**Probably yes** Reason: radiological reports were used; for other confounders it is not sure how they were assessed.	**Definitely no** Reason: no adjustment for confounding	**Probably no** Reason: due to retrospective nature of the study, it is possible that bleeding events were missed.	**No information** Reason: Follow-up period was not reported by anticoagulatn group. Loss to follow-up is not reported. Follow-up intervals (imaging) were not standardized.	**No information**	**High (all outcomes)**
Naymagon (2021 ––B)	**Probably no** Reason: Time frame might be different between the groups, there	**Probably yes** Reason: No information (initial long-term AC used	**Definitely yes** Reason: It is not likely that the outcome measure major bleeding was	**Probably yes** Reason: radiological reports were used; for other confounders it is not sure how	**Definitely no** Reason: no adjustment for confounding	**Probably no** Reason: due to retrospective nature of the study, it is possible that	**Probably no** Reason: length of follow-up differed between the groups. Loss to follow-up is	**No information**	**High (all outcomes)**

	might have been indication bias. Patients with short follow-up (imaging < 3 months) were excluded, thus patients who may have died of acute complication of PVT were not included.	in each instance was recorded), but it is most likely that exposure is determined correctly.	present at the start of the study.	they were assessed.		bleeding events were missed.	not reported. Follow-up intervals (imaging) were not standardized.		
Zhang (2023)	**Probably no** Reason: Time frame might be different between the groups, there might have been indication bias.	**Probably yes** Reason: Information was collected from medical records, and it is most likely that exposure is determined correctly.	**Definitely yes** Reason: It is not likely that the outcome measure major bleeding was present at the start of the study.	**Probably yes** Reason: Information was collected from medical records, and confounders might be determined correctly	**Definitely no** Reason: No adjustment for confounding	**Probably no** Reason: Due to retrospective nature of the study, it is possible that bleeding events are missed.	**No information** Reason: Follow-up period was not reported by anticoagulatn group. Loss to follow-up is not reported.	**No information**	**High (all outcomes)**

Table of excluded studies
Search I – Systematic reviews and RCTs

Reference	Reason for exclusion
Ding H, Zhang Y, Zhao L, Wu S, Liu J, Wang C, Pei T, Su Y. What intervention regimen is most effective prevention for Portal venous system thrombosis after splenectomy in cirrhotics patients with Portal hypertension? Systematic review and network meta-analysis. Pharmacol Res. 2020 Jul;157:104825. doi: 10.1016/j.phrs.2020.104825. Epub 2020 Apr 21. PMID: 32330553.	Wrong comparison
Yao W, Feng Y, Liu T, Li W, Zhang M, Yao Y, Wu S. Rivaroxaban versus low-molecular weight heparin plus warfarin prevents portal vein system thrombosis after splenectomy and pericardial devascularization: A randomized clinical trial. EXCLI J. 2021 Mar 4;20:537-549. doi: 10.17179/excli2020-3120. PMID: 33883982; PMCID: PMC8056059.	Wrong population, wrong outcome
Yao C, Zhao M, Ibrahim B, Saab S. Anticoagulation for the Treatment of Portal Vein Thrombosis in Cirrhosis: A Systematic Review and Meta-Analysis of Comparative Studies. J Clin Exp Hepatol. 2023 May-Jun;13(3):404-413. doi: 10.1016/j.jceh.2022.12.016. Epub 2023 Jan 3. PMID: 37250883; PMCID: PMC10213860.	Wrong comparison (anticoagulation vs no treatment)
Li Z, Xu W, Wang L, Chai L, Ageno W, Romeiro FG, Li H, Qi X. Risk of Bleeding in Liver Cirrhosis Receiving Direct Oral Anticoagulants: A Systematic Review and Meta-analysis. Thromb Haemost. 2023 Jun 19. doi: 10.1055/s-0043-1770100. Epub ahead of print. PMID: 37336474.	Wrong population
Guerrero A, Campo LD, Piscaglia F, Scheiner B, Han G, Violi F, Ferreira CN, Téllez L, Reiberger T, Basili S, Zamora J, Albillos A; Baveno Cooperation: an EASL consortium. Anticoagulation improves survival in patients with cirrhosis and portal vein thrombosis: The IMPORTAL competing-risk meta-analysis. J Hepatol. 2023 Jul;79(1):69-78. doi: 10.1016/j.jhep.2023.02.023. Epub 2023 Feb 28. PMID: 36858157.	Wrong comparison (anticoagulation vs no treatment)
Candeloro M, Valeriani E, Monreal M, Ageno W, Riva N, Schulman S, Bang SM, Mellado M, Díaz-Peromingo JA, Moisés J, Díaz-Brasero AM, Garcia-Pagan JC, Perez-Campuzano V, Senzolo M, De Gottardi A, Di Nisio M. Clinical course and treatment of incidentally detected splanchnic vein thrombosis: an individual patient data meta-analysis. J Thromb Haemost. 2023 Jun;21(6):1592-1600. doi: 10.1016/j.jtha.2023.03.002. Epub 2023 Mar 11. PMID: 36907381.	Wrong comparison
Zhang Z, Zhao Y, Han B, Zhu Z, Sun L, Cui X. The Efficacy and Safety of Anticoagulants in the Treatment of Cirrhotic Portal Vein Thrombosis: A Systematic Review and Meta-Analysis. Clin Appl Thromb Hemost. 2022 Jan-Dec;28:10760296221104797. doi: 10.1177/10760296221104797. PMID: 35656719; PMCID: PMC9168872.	Incomplete search strategy/search strategy is very specific
Koh JH, Liew ZH, Ng GK, Liu HT, Tam YC, De Gottardi A, Wong YJ. Efficacy and safety of direct oral anticoagulants versus vitamin K antagonist for portal vein thrombosis in cirrhosis: A systematic review and meta-analysis. Dig Liver Dis. 2022	Wrong population

Jan;54(1):56-62. doi: 10.1016/j.dld.2021.07.039. Epub 2021 Aug 13. PMID: 34393072.	
Candeloro M, Valeriani E, Monreal M, Ageno W, Riva N, Lopez-Reyes R, Peris ML, Beyer Westendorf J, Schulman S, Rosa V, López-Núñez JJ, Garcia-Pagan JC, Magaz M, Senzolo M, De Gottardi A, Di Nisio M. Anticoagulant therapy for splanchnic vein thrombosis: an individual patient data meta-analysis. Blood Adv. 2022 Aug 9;6(15):4516-4523. doi: 10.1182/bloodadvances.2022007961. PMID: 35613465; PMCID: PMC9636325.	Missing information on included studies (subgroup analysis on DOAC)
Valeriani E, Di Nisio M, Riva N, Cohen O, Porreca E, Senzolo M, De Gottardi A, Magaz M, Garcia-Pagan JC, Ageno W. Anticoagulant Treatment for Splanchnic Vein Thrombosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis. Thromb Haemost. 2021 Jul;121(7):867-876. doi: 10.1055/s-0040-1722192. Epub 2021 Feb 1. PMID: 33525037.	Included case series
Ng CH, Tan DJH, Nistala KRY, Syn N, Xiao J, Tan EXX, Woo FZ, Chew NWS, Huang DQ, Dan YY, Sanyal AJ, Muthiah MD. A network meta-analysis of direct oral anticoagulants for portal vein thrombosis in cirrhosis. Hepatol Int. 2021 Oct;15(5):1196-1206. doi: 10.1007/s12072-021-10247-x. Epub 2021 Aug 21. PMID: 34417718.	Included retracted RCT of Hanafy, no update possible
Ghazaleh S, Beran A, Aburayyan K, Nehme C, Patel D, Khader Y, Sharma S, Aziz M, Abdel-Aziz Y, Hammad T, Nawras A. Efficacy and safety of anticoagulation in non-malignant portal vein thrombosis in patients with liver cirrhosis: a systematic review and meta-analysis. Ann Gastroenterol. 2021;34(1):104-110. doi: 10.20524/aog.2020.0544. Epub 2020 Oct 2. PMID: 33414629; PMCID: PMC7774659.	Wrong comparison
Qi X, De Stefano V, Li H, Dai J, Guo X, Fan D. Anticoagulation for the treatment of portal vein thrombosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. Eur J Intern Med. 2015 Jan;26(1):23-9. doi: 10.1016/j.ejim.2014.12.002. Epub 2015 Jan 5. PMID: 25566699.	Wrong comparison
Semmler G, Lindorfer A, Schäfer B, Bartl S, Hametner-Schreil S, Gensluckner S, Balcar L, Pomej K, Lampichler K, Trauner M, Aigner E, Datz C, Zoller H, Hofer H, Schöfl R, Mandorfer M, Reiberger T, Scheiner B. Outcome of Budd-Chiari Syndrome Patients Treated With Direct Oral Anticoagulants: An Austrian Multicenter Study. Clin Gastroenterol Hepatol. 2023 Apr;21(4):978-987.e2. doi: 10.1016/j.cgh.2022.04.024. Epub 2022 May 6. PMID: 35533994.	Retrospective study, insufficient information on the control group
Sharma S, Kumar R, Rout G, Gamanagatti SR, Shalimar. Dabigatran as an oral anticoagulant in patients with Budd-Chiari syndrome post-percutaneous endovascular intervention. J Gastroenterol Hepatol. 2020 Apr;35(4):654-662. doi: 10.1111/jgh.14843. Epub 2019 Nov 25. PMID: 31476024.	Included in Valeriani, 2021

Salim S, Ekberg O, Elf J, Zarrouk M, Gottsäter A, Acosta S. Evaluation of direct oral anticoagulants and vitamin K antagonists in mesenteric venous thrombosis. Phlebology. 2019 Apr;34(3):171-178. doi: 10.1177/0268355518779517. Epub 2018 May 31. PMID: 29848218.	Switch over study
Hanafy AS, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis. Vascul Pharmacol. 2019 Feb;113:86-91. doi: 10.1016/j.vph.2018.05.002. Epub 2018 Jun 7. Retraction in: Vascul Pharmacol. 2023 Jan 12;:107142. PMID: 29886103.	Retracted article
Janczak DT, Mimier MK, McBane RD, Kamath PS, Simmons BS, Bott-Kitslaar DM, Lenz CJ, Vargas ER, Hodge DO, Wysokinski WE. Rivaroxaban and Apixaban for Initial Treatment of Acute Venous Thromboembolism of Atypical Location. Mayo Clin Proc. 2018 Jan;93(1):40-47. doi: 10.1016/j.mayocp.2017.10.007. Epub 2017 Dec 6. PMID: 29217335.	Wrong population
Yin Y, Wang L, Gao F, Liu L, Qi X. Anticoagulation Therapy for Splanchnic Vein Thrombosis Associated With Acute Pancreatitis: A Systematic Review and Meta-Analysis. Clin Appl Thromb Hemost. 2023 Jan-Dec;29:10760296231188718. doi: 10.1177/10760296231188718. PMID: 37461391; PMCID: PMC10357047.	Wrong comparison
Sissingh NJ, Groen JV, Koole D, Klok FA, Boekestijn B, Bollen TL, van Santvoort HC, Verdonk RC, Bonsing BA, van Eijck CHJ, van Hooft JE, Mieog JSD; Dutch Pancreatitis Study Group. Therapeutic anticoagulation for splanchnic vein thrombosis in acute pancreatitis: A systematic review and meta-analysis. Pancreatology. 2022 Mar;22(2):235-243. doi: 10.1016/j.pan.2021.12.008. Epub 2021 Dec 22. PMID: 35012902.	Wrong comparison
Ghazaleh S, Chuang J, Sayeh W, Iqbal A, Beran A, Khader Y, Burmeister C, Aziz M, Assaly R, Nawras A. Comparative Efficacy of Anticoagulant Medications in Nonmalignant Portal Vein Thrombosis in Liver Cirrhosis-A Systematic Review and Network Meta-analysis. Am J Ther. 2022 Jul 8. doi: 10.1097/MJT.0000000000001538. Epub ahead of print. PMID: 36927678.	Wrong publication type
Anis FS, Adiamah A, Lobo DN, Sanyal S. Incidence and treatment of splanchnic vein thrombosis in patients with acute pancreatitis: A systematic review and meta-analysis. J Gastroenterol Hepatol. 2022 Mar;37(3):446-454. doi: 10.1111/jgh.15711. Epub 2021 Nov 3. PMID: 34657310.	Wrong comparison
Wang L, Guo X, Xu X, De Stefano V, Plessier A, Noronha Ferreira C, Qi X. Anticoagulation Favors Thrombus Recanalization and Survival in Patients With Liver Cirrhosis and Portal Vein Thrombosis: Results of a Meta-Analysis. Adv Ther. 2021 Jan;38(1):495-520. doi: 10.1007/s12325-020-01550-4. Epub 2020 Nov 5. PMID: 33155180; PMCID: PMC7854392.	Missing studies compared to other systematic reviews
Gupta S, Hidalgo J, Singh B, Iyer A, Yang Y, Short A, Singh S, Bhatt H, Gupta S. Usage of Direct Acting Oral Anticoagulants in Cirrhotic and Non-Cirrhotic Portal Vein Thrombosis: A Systematic Review. Cureus. 2021 Aug 5;13(8):e16922. doi:	No meta-analysis

10.7759/cureus.16922. PMID: 34367844; PMCID: PMC8342267.	
Coons EM, Staubes BA, Casey AL, Elagizi-Youssef SA, Mohammed AE, Sharma N, Kline ER. Direct Oral Anticoagulants Versus Warfarin for Treatment of Thrombosis or Atrial Fibrillation in Patients With Cirrhosis: A Retrospective Cohort Study. Ann Pharmacother. 2022 May;56(5):533-540. doi: 10.1177/10600280211025050. Epub 2021 Sep 1. PMID: 34470525.	No meta-analysis
Gao Y, Liu H, Tang F, Zhang X, Li F, Ye Q, Yuan H, Lv H, Han T. Efficacy and safety of anticoagulants in liver cirrhosis patients with portal vein thrombosis: A meta-analysis. Clin Res Hepatol Gastroenterol. 2021 Mar;45(2):101649. doi: 10.1016/j.clinre.2021.101649. Epub 2021 Feb 16. PMID: 33601064.	Wrong comparison
Dong S, Qi H, Li Y, Men P, Alifu M, Zhang Y, Li Y, Zhao R. A systematic review and meta-analysis of anticoagulation therapy for portal vein thrombosis in patients with cirrhosis: to treat or not to treat? Hepatol Int. 2021 Dec;15(6):1356-1375. doi: 10.1007/s12072-021-10233-3. Epub 2021 Sep 6. PMID: 34487316.	Wrong comparison
Chen H, Lei J, Liang S, Luo G, Deng M, Lü M. Safety and Efficacy of Anticoagulation in Patients with Cirrhosis: A Meta-Analysis. Can J Gastroenterol Hepatol. 2021 Apr 21;2021:8859602. doi: 10.1155/2021/8859602. PMID: 34007837; PMCID: PMC8102101.	No complete information on search strategy
Mohan BP, Aravamudan VM, Khan SR, Ponnada S, Asokkumar R, Adler DG. Treatment response and bleeding events associated with anticoagulant therapy of portal vein thrombosis in cirrhotic patients: Systematic review and meta-analysis. Ann Gastroenterol. 2020 Sep-Oct;33(5):521-527. doi: 10.20524/aog.2020.0503. Epub 2020 May 30. PMID: 32879600; PMCID: PMC7406805.	Included studies which were also included in Zhang (2022), additional study was of Scheiner (no-comparative study) and did not include Ilzewics.
Di Nisio M, Valeriani E, Riva N, Schulman S, Beyer-Westendorf J, Ageno W. Anticoagulant therapy for splanchnic vein thrombosis: ISTH SSC Subcommittee Control of Anticoagulation. J Thromb Haemost. 2020 Jul;18(7):1562-1568. doi: 10.1111/jth.14836. PMID: 32619346.	Guidance document
Priyanka P, Kupec JT, Krafft M, Shah NA, Reynolds GJ. Newer Oral Anticoagulants in the Treatment of Acute Portal Vein Thrombosis in Patients with and without Cirrhosis. Int J Hepatol. 2018 Jun 5;2018:8432781. doi: 10.1155/2018/8432781. PMID: 29973997; PMCID: PMC6008786.	Narrative review
Hoolwerf EW, Kraaijpoel N, Büller HR, van Es N. Direct oral anticoagulants in patients with liver cirrhosis: A systematic review. Thromb Res. 2018 Oct;170:102-108. doi: 10.1016/j.thromres.2018.08.011. Epub 2018 Aug 17. PMID: 30153564.	Wrong population
Zhang W, Zhou DM, Li Y. [Clinical effect of low-molecular-weight heparin in prevention and treatment of liver cirrhosis and portal vein thrombosis after splenectomy: a systematic review and meta-analysis]. Zhonghua Gan Zang Bing Za Zhi. 2016 Oct 20;24(10):732-737. Chinese. doi: 10.3760/cma.j.issn.1007-3418.2016.10.004. PMID: 27938557.	Wrong language

Lv Y, Bai W, Li K, Wang Z, Guo W, Luo B, Wang J, Wang Q, Wang E, Xia D, Li X, Yuan J, Han N, Niu J, Yin Z, Fan D, Han G. Anticoagulation and Transjugular Intrahepatic Portosystemic Shunt for the Management of Portal Vein Thrombosis in Cirrhosis: A Prospective Observational Study. Am J Gastroenterol. 2021 Jul 1;116(7):1447-1464. doi: 10.14309/ajg.0000000000001194. Erratum in: Am J Gastroenterol. 2022 Jan 1;117(1):200. PMID: 33630766.	Wrong intervention/comparison
Li A, Zhang MC, Li P, Eshaghpour A, Li K, Carrier M, Wells P, Crowther MA. Direct oral anticoagulants for the treatment of splanchnic vein thrombosis - A systematic review and meta-analysis. Thromb Res. 2023 Sep;229:209-218. doi: 10.1016/j.thromres.2023.06.003. Epub 2023 Jun 20. PMID: 37544136.	Incomplete search strategy
Tang K, Weinberg EM. Direct oral anticoagulants in the treatment of portal vein thrombosis in patients with portal hypertension. Clin Liver Dis (Hoboken). 2023 Jul 10;22(2):37-41. doi: 10.1097/CLD.0000000000000063. PMID: 37663556; PMCID: PMC10473309.	No systematic review with meta-analysis, wrong publication type

Search II – Observational studies

Reference	Reason for exclusion
Bergère M, Erard-Poinsot D, Boillot O, Valette PJ, Guillaud O, Chambon-Augoyard C, Dumortier J. Portal vein thrombosis and liver cirrhosis: Long-term anticoagulation is effective and safe. Clin Res Hepatol Gastroenterol. 2019 Aug;43(4):395-402. doi: 10.1016/j.clinre.2018.11.011. Epub 2018 Dec 18. PMID: 30578107.	wrong comparison
Serrao A, Merli M, Lucani B, Aprile F, Fiori L, Gioia S, Breccia M, Riggio O, Chistolini A. Outcomes of long-term anticoagulant treatment for the secondary prophylaxis of splanchnic venous thrombosis. Eur J Clin Invest. 2021 Jan;51(1):e13356. doi: 10.1111/eci.13356. Epub 2020 Aug 11. PMID: 33180323.	wrong study population, wrong comparison
Pettinari I, Vukotic R, Stefanescu H, Pecorelli A, Morelli M, Grigoras C, Sparchez Z, Andreone P, Piscaglia F; BO-LIVES (BOlogna LIVEr vascular Studies). Clinical Impact and Safety of Anticoagulants for Portal Vein Thrombosis in Cirrhosis. Am J Gastroenterol. 2019 Feb;114(2):258-266. doi: 10.1038/s41395-018-0421-0. PMID: 30538290.	wrong comparison
K T, Chan SJ, Varghese C, Lim WB, Cheemungtoo GM, Akter N, Nayar M, Pandanaboyana S. A selective anticoagulation policy for splanchnic vein thrombosis in acute pancreatitis is associated with favourable outcomes: experience from a UK tertiary referral centre. HPB (Oxford). 2022 Nov;24(11):1937-1943. doi: 10.1016/j.hpb.2022.06.003. Epub 2022 Jun 16. PMID: 35786365.	wrong comparison
Saleh S, Dalal S, Desai A, Thomas C, Chitsaz E. Outcomes of Anticoagulation in Patients With Splanchnic Vein Thrombosis From Acute Pancreatitis: A Population-Based Nationwide Retrospective Cohort Study. Pancreas. 2022 Sep 1;51(8):e105-e106. doi: 10.1097/MPA.0000000000002122. PMID: 36607956.	wrong publication type
Acuna-Villaorduna A, Tran V, Gonzalez-Lugo JD, Azimi-Nekoo E, Billett HH. Natural history and clinical outcomes in patients with portal vein thrombosis by etiology: A	wrong comparison

retrospective cohort study. Thromb Res. 2019 Feb;174:137-140. doi: 10.1016/j.thromres.2018.12.019. Epub 2018 Dec 27. PMID: 30597344.	
Barbui T, De Stefano V, Carobbio A, Iurlo A, Alvarez-Larran A, Cuevas B, Ferrer Marín F, Vannucchi AM, Palandri F, Harrison C, Sibai H, Griesshammer M, Bonifacio M, Elli EM, Trotti C, Koschmieder S, Carli G, Benevolo G, Ianotto JC, Goel S, Falanga A, Betti S, Cattaneo D, Arellano-Rodrigo E, Mannelli L, Vianelli N, Doyle A, Gupta V, Wille K, Tremblay D, Mascarenhas J. Direct oral anticoagulants for myeloproliferative neoplasms: results from an international study on 442 patients. Leukemia. 2021 Oct;35(10):2989-2993. doi: 10.1038/s41375-021-01279-1. Epub 2021 May 19. PMID: 34012132; PMCID: PMC8132485.	wrong publication type
Naymagon L, Tremblay D, Mascarenhas J, Schiano T. Characteristics, anticoagulation, and outcomes of portal vein thrombosis after intra-abdominal surgery. Surgery. 2021 May;169(5):1175-1181. doi: 10.1016/j.surg.2020.11.016. Epub 2020 Dec 24. PMID: 33358635.	wrong outcomes
Hajibandeh S, Hajibandeh S, Agrawal S, Irwin C, Obeidallah R, Subar D. Anticoagulation Versus No Anticoagulation for Splanchnic Venous Thrombosis Secondary to Acute Pancreatitis: Do We Really Need to Treat the Incidental Findings? Pancreas. 2020 Oct;49(9):e84-e85. doi: 10.1097/MPA.0000000000001644. PMID: 33003093.	wrong publication type
Noronha Ferreira C, Cortez-Pinto H, Serejo F, Velosa J, Marinho RT. Anticoagulation in patients with cirrhosis and portal vein thrombosis: Safety and beneficial effect on OLT-free survival. Liver Int. 2019 Oct;39(10):2002. doi: 10.1111/liv.14231. Epub 2019 Sep 18. PMID: 31461802.	wrong publication type
Andraska E, Haga L, Reitz K, Li X, Ramos R, Avgerinos E, Singh M, Eslami M, Makaroun M, Chaer R. Acute superior mesenteric venous thrombosis results in high rates of readmission and morbidity. J Vasc Surg Venous Lymphat Disord. 2020 Sep;8(5):748-755. doi: 10.1016/j.jvsv.2020.01.007. Epub 2020 Mar 3. PMID: 32139329; PMCID: PMC7434641.	wrong comparison

Literature search strategy

Zoekverantwoording

Algemene informatie

Richtlijn: NIV – Antitrombotisch beleid	
Uitgangsvraag: UV8 Wat is de optimale antistollingsbehandeling van patiënten met buikvene trombose	
Database(s): Ovid/Medline, Embase	Datum: 1-8-2023,30-10-2023
Periode: 2019-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp https://rayyan.ai/reviews/739844?	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	

Toelichting:
30-10-2023
Er wordt gekozen om de SR van Valeriani (2019) als uitgangspunt te nemen. De zoekstrategie wordt geüpdatet en de observationele studies worden toegevoegd.
De twee sleutelartikelen worden gevonden:

- Semmler (2023): Outcome of Budd-Chiari Syndrome Patients Treated With Direct Oral Anticoagulants: An Austrian Multicenter Study, PMID: 35533994, zie bijlage.
- Salim (2019): Evaluation of direct oral anticoagulants and vitamin K antagonists in mesenteric venous thrombosis, PMID: , 29848218, zie bijlage.

1-8-2023
Voor deze vraag is gezocht met de volgende concepten:
Buikvene trombose EN antistolling
Omdat een van de sleutelartikelen niet wordt gevonden als met DOACs wordt gezocht, is ervoor gekozen om te zoeken met antistolling.
Vanwege de aantallen worden alleen de SRs, clinical trials en RCTs aangeboden. Zo nodig kunnen later de overige observationele studies worden toegevoegd.

Zoekopbrengst

30-10-2023 Vanaf 2019	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld t.ov. Rayyan 1-8-2023**
SRs	141	52	10
RCTs	158	41	11
Observationele studies	511	126	532
Overig	810	219	
Totaal			553
1-8-2023	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs	247	84	254
RCTs	377	103	415
Observationele studies			
Overig			
Totaal			669

5 ***Zoekstrategie***
Embase

No.	Query	Results
#19	#17 AND #18 sleutelartikelen gevonden	3
#18	#9 OR #10	624

#17	#15 AND #16	3
#16	#9 OR #10 OR #11	1707
#15	#12 OR #13 OR #14 sleutelartikelen	3
#14	'anticoagulant therapy for splanchnic vein thrombosis: a systematic review and meta-analysis' AND 2021 NOT [2020]/py	1
#13	'rivaroxaban for the treatment of noncirrhotic splanchnic vein thrombosis: an interventional prospective cohort study'	1
#12	'randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis'	1
#11	#4 AND (#7 OR #8) NOT #9 NOT #10 Observationele studies	1083
#10	#4 AND #6 NOT #9 Clinical trials, RCTs	377
#9	#4 AND #5 SR	247
#8	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	14286706

#7	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6767914
#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3302394
#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#4	#3 AND [2008-2023]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	3567
#3	#1 AND #2	4816
#2	'direct oral anticoagulant'/exp OR 'direct oral anticoagulant agent'/exp OR 'anticoagulant agent'/exp OR 'apixaban'/exp OR 'non vitamin k antagonist oral anticoagulant'/exp OR 'thrombin inhibitor'/exp OR 'edoxaban'/exp OR 'rivaroxaban'/exp OR 'dabigatran'/exp OR 'thrombin inhibitor':ti,ab,kw OR 'aboxoma':ti,ab,kw OR 'apixaban':ti,ab,kw OR 'apixaben':ti,ab,kw OR doac*:ti,ab,kw OR 'bms 562247':ti,ab,kw OR 'bms562247':ti,ab,kw OR 'eliques':ti,ab,kw OR 'eliquis':ti,ab,kw OR 'lunast':ti,ab,kw OR 'pf 0465257':ti,ab,kw OR 'pf0465257':ti,ab,kw OR 'tah 3311':ti,ab,kw OR 'tah3311':ti,ab,kw OR 'bibr 953':ti,ab,kw OR 'bibr953':ti,ab,kw OR 'dabigatran':ti,ab,kw OR 'du 176':ti,ab,kw OR 'du 176b':ti,ab,kw OR	812381

	'du176':ti,ab,kw OR 'du176b':ti,ab,kw OR 'edoxaban':ti,ab,kw OR 'endoxaban':ti,ab,kw OR 'lixiana':ti,ab,kw OR 'roteas':ti,ab,kw OR 'savaysa':ti,ab,kw OR 'assubex':ti,ab,kw OR 'ast 8294':ti,ab,kw OR 'ast8294':ti,ab,kw OR 'bay 59 7939':ti,ab,kw OR 'bay 597939':ti,ab,kw OR 'bay59 7939':ti,ab,kw OR 'bay597939':ti,ab,kw OR 'bs 112':ti,ab,kw OR 'bs112':ti,ab,kw OR 'dst 8294':ti,ab,kw OR 'dst8294':ti,ab,kw OR 'jnj 39039039':ti,ab,kw OR 'jnj39039039':ti,ab,kw OR 'kriva':ti,ab,kw OR 'naxat':ti,ab,kw OR 'rivaro':ti,ab,kw OR 'rivarolto':ti,ab,kw OR 'rivaroxaban':ti,ab,kw OR 'rivaxa':ti,ab,kw OR 'throsaben':ti,ab,kw OR 'xanirva':ti,ab,kw OR 'xarelto':ti,ab,kw OR 'xerdoxo':ti,ab,kw OR 'xindus':ti,ab,kw	
#1	'budd chiari syndrome'/exp OR 'mesenteric thrombosis'/exp OR 'portal vein thrombosis'/exp OR 'splanchnic vein thrombosis'/exp OR (('hepatic portal vein'/exp OR 'mesenteric vein'/exp OR 'splenic vein'/exp) AND 'thrombosis'/exp) OR (((splanchnic OR splenic OR 'vena lienalis' OR mesenter* OR abdom* OR portal OR porto OR hepatic) NEAR/3 (thromb* OR occlusi*)):ti,ab,kw) OR 'pylethromb*':ti,ab,kw OR 'budd-chiari':ti,ab,kw OR ((chiari NEAR/2 (deform* OR disease* OR syndrom*)):ti,ab,kw) OR 'endophlebitis obliterans hepatica':ti,ab,kw OR 'splenic vein thrombosis'/exp	44815

Ovid/Medline

#	Searches	Results
9	(5 and 7) not 8 Clinical trials, RCTs	103
8	5 and 6 SR	84
7	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2616982
6	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data	684473

	source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	1007
4	limit 3 to yr="2008 - 2023"	1132
3	1 and 2	1885
2	exp Anticoagulants/ or Rivaroxaban/ or exp Dabigatran/ or thrombin inhibitor.ti,ab,kf. or aboxoma.ti,ab,kf. or apixaban.ti,ab,kf. or apixaben.ti,ab,kf. or doac*.ti,ab,kf. or bms 562247.ti,ab,kf. or bms562247.ti,ab,kf. or eliques.ti,ab,kf. or eliquis.ti,ab,kf. or lunast.ti,ab,kf. or "pf 0465257".ti,ab,kf. or pf0465257.ti,ab,kf. or tah 3311.ti,ab,kf. or tah3311.ti,ab,kf. or bibr 953.ti,ab,kf. or bibr953.ti,ab,kf. or dabigatran.ti,ab,kf. or du 176.ti,ab,kf. or du 176b.ti,ab,kf. or du176.ti,ab,kf. or du176b.ti,ab,kf. or edoxaban.ti,ab,kf. or endoxaban.ti,ab,kf. or lixiana.ti,ab,kf. or roteas.ti,ab,kf. or savaysa.ti,ab,kf. or assubex.ti,ab,kf. or ast 8294.ti,ab,kf. or ast8294.ti,ab,kf. or bay 59 7939.ti,ab,kf. or bay 597939.ti,ab,kf. or bay59 7939.ti,ab,kf. or bay597939.ti,ab,kf. or bs 112.ti,ab,kf. or bs112.ti,ab,kf. or dst 8294.ti,ab,kf. or dst8294.ti,ab,kf. or jnj 39039039.ti,ab,kf. or jnj39039039.ti,ab,kf. or kriva.ti,ab,kf. or naxat.ti,ab,kf. or rivaro.ti,ab,kf. or rivarolto.ti,ab,kf. or rivaroxaban.ti,ab,kf. or rivaxa.ti,ab,kf. or throsaben.ti,ab,kf. or xanirva.ti,ab,kf. or xarelto.ti,ab,kf. or xerdoxo.ti,ab,kf. or xindus.ti,ab,kf.	247867
1	Budd-Chiari Syndrome/ or exp Mesenteric Vascular Occlusion/ or ((Portal System/ or Mesenteric Veins/ or Portal Vein/ or Splenic Vein/) and exp Thrombosis/) or ((splanchnic or splenic or vena lienalis or mesenter* or abdom* or portal or porto or hepatic) adj3 (thromb* or occlusi*)).ti,ab,kf. or pylethromb*.ti,ab,kf. or budd-chiari.ti,ab,kf. or (chiari adj2 (deform* or disease* or syndrom*)).ti,ab,kf. or endophlebitis obliterans hepatica.ti,ab,kf.	27836

Module 7 Antitrombotisch beleid na bariatrische chirurgie

Autorisatie en geldigheid

Autorisatiedatum:	*pending*
Eerstvolgende beoordeling actualiteit	volgende cyclus binnen het cluster Antitrombotisch beleid
Geautoriseerd door:	*pending*
Belangrijkste wijzigingen t.o.v. vorige versie:	n.v.t., het betreft een nieuwe module
Herbevestiging:	n.v.t.
Regiehouder:	Nederlandse Internisten Vereniging

Uitgangsvraag

Wat is de optimale therapeutische antistollingsbehandeling bij patiënten die bariatrische chirurgie hebben ondergaan?

Introduction

Bariatric surgery is a common and effective treatment for reducing weight and preventing obesity-related health complications. Patients undergoing bariatric surgery either already had anticoagulant treatment for prevention of stroke when they have atrial fibrillation or are treated for venous thromboembolism, or are at increased risk of peri-operative thromboembolism and many patients eventually develop an indication for anticoagulant therapy, such as venous thromboembolism (VTE), atrial fibrillation, or peripheral arterial disease. Direct oral anticoagulants (DOACs) are effective at treating VTE and preventing stroke and systemic embolization in patients with non-valvular atrial fibrillation where they have similar efficacy as vitamin K antagonists (VKA) with an enhanced safety profile. DOACs are absorbed in the upper gastrointestinal (GI) tract, which is altered by the most common bariatric surgical procedures including Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and duodenal switch. Postoperative changes in GI motility and the luminal absorptive surface may reduce the absorption of DOACs, thereby placing patients at risk of avoidable thrombotic complications. Similarly, use of VKAs after bariatric surgery is complicated by labile international normalized ratios (INRs) resulting in frequent over-or under-anticoagulation.

Search and select

A systematic review of the literature was performed to answer the following question: What is the effect of adjustment in DOAC-therapy compared to standard of care (no adjustment in DOAC-therapy), in adult patients who have undergone bariatric surgery (gastric bypass) and had an indication for full-dose of DOACs preoperatively?

P	**(Patients)**	Adult patients who have undergone bariatric surgery (gastric bypass or gastric sleeve) and had an indication for therapeutic doses of DOACs preoperatively
I	**(Intervention)**	Adjusted DOAC-therapy (DOAC to VKA or to another DOAC)
C	**(Comparison)**	Standard of care (no adjustment in DOAC-therapy**)**

O	**(Outcomes)**	venous thromboembolism (VTE), arterial thromboembolism (ATE), major bleeding, clinical relevant non-major bleeding (CRNMB), anti-Xa plasma levels, quality of life

Relevant outcome measures

The guideline development group considered VTE, ATE and major bleeding as critical outcome measures for decision making and CRNMB, anti-Xa plasma levels and quality of life as important outcome measures for decision making.

The working group defined the outcomes as follows:

- VTE: symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE)
- Major bleeding: fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin levels of 1.24 mmol/L (20 g/L or greater) or more, or leading to a transfusion of 2 U or more of whole blood or red cells, as defined by International Society on Thrombosis and Haemostasis;

A priori, the working group did not define the other outcome measures listed above but used the definitions used in the studies.

The working group defined the following as a minimal clinically (patient) important difference:

- VTE, ATE, major bleeding and CRNMB: risk difference of 3%*
- For all other outcome measures, the default thresholds proposed by the international GRADE working group were used as a threshold for clinically relevant differences: a 25% difference in relative risk (RR) for dichotomous outcomes (RR <0.8 or RR >1.25), and 0.5 standard deviations (SD) for continuous outcomes.

**Based on the differences applied in the guidelines on thromboprophylaxis in patients with COVID-19. This working group derived the minimal clinically (patient) important differences from the ACCP (2012).*

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until August 21th 2024. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 1361 hits. For the selection of relevant articles, ASReview was used. ASReview uses state-of-the-art active learning techniques to select the most relevant articles from a large number of potential hits. To run the program, priors need to be indicated. A prior is an article that is found in the current number of hits and complies (or best matches) to the current selection criteria. The standard (default) model specifications were used for the screening for these papers.

Studies were selected based on the following criteria: (systematic reviews) of RCTs or cohort studies comparing adjusted DOAC-therapy (DOAC to VKA or another DOAC) in adult patients who have undergone bariatric surgery (gastric bypass, sleeve gastrectomy) and had an indication for full-dose of DOACs preoperatively.

Eight studies were initially selected based on title and abstract screening, using ASReview. After reading the full text, all studies were excluded (see the table with reasons for exclusion under the tab Methods), and no studies were included.

Results
No study could be included in the analysis of the literature.

Summary of literature

Description of studies
No study could be included in the analysis of the literature.

Results
No study could be included in the analysis of the literature.

Level of evidence of the literature
No study could be included in the analysis of the literature.

Conclusions

No GRADE	No evidence was found regarding the effect of adjustment of DOAC-therapy on outcome when compared with no adjustment of DOAC-therapy in bariatric patients having an indication for therapeutic dose of DOACs preoperatively. *Sources: none*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Er is geen studie beschikbaar waarin het effect van een aanpassing in de behandeling met directe orale anticoagulantia (DOAC) is onderzocht in patiënten die bariatrische chirurgie hebben ondergaan en preoperatief een indicatie hadden voor een therapeutische dosis DOAC's. Hierdoor is het niet mogelijk om een conclusie te trekken over het effect van het aanpassen van de DOAC-therapie, vergeleken met het niet aanpassen van de DOAC-therapie op de cruciale uitkomstmaten arteriële en veneuze trombo-embolieën (ATE en VTE) en majeure bloedingen. Hetzelfde geldt voor het effect op de belangrijke uitkomstmaten klinisch relevante niet-majeure bloedingen, anti-Xa spiegels en kwaliteit van leven. De overall bewijskracht is hiermee zeer laag. Er is duidelijk sprake van een kennisvraag.

Deze module gaat niet in op het periprocedurele beleid voor patiënten die DOAC's gebruiken en bariatrische chirurgie ondergaan. Aanbevelingen daarover zijn opgenomen in de module Periprocedureel beleid DOAC's.

Indirect bewijs
Uit de systematische zoekstrategie kwamen twee studies naar voren, die hebben gekeken naar het effect van DOAC's versus warfarine in patiënten die bariatrische chirurgie hebben ondergaan en postoperatief een indicatie voor antistollingsbehandeling hebben ontwikkeld (Hendricks, 2020 en Srivastava, 2021). Hendricks (2020) voerde een gematchte cohortstudie uit naar de effectiviteit en veiligheid van antistollingsbehandeling in patiënten met atriumfibrilleren die bariatrische chirurgie hebben ondergaan, vergeleken met een groep patiënten die geen bariatrische chirurgie ondergingen. In een secundaire analyse keken ze naar het effect van een behandeling met DOAC's versus een behandeling met warfarine in de patiënten die bariatrische chirurgie hebben ondergaan, op de uitkomst infarct/systemische embolie, majeure bloeding en mortaliteit. De bewijskracht is echter zeer laag vanwege ernstige imprecisie en het risico op bias. Daarom is er op basis van deze gegevens geen conclusie te trekken over het effect van de behandeling met DOAC's versus warfarine in patiënten die na bariatrische chirurgie een indicatie voor

antistollingsbehandeling ontwikkelen. Omdat er geen RCT's beschikbaar zijn die het gebruik van DOAC's direct vergelijken met warfarine in patiënten die bariatrische chirurgie hebben ondergaan, heeft Srivastava (2021) de gegevens die beschikbaar zijn voor de behandeling met DOAC's vergeleken met de gegevens die beschikbaar zijn voor behandeling met warfarine. Ook hiervoor geldt dat de bewijskracht zeer laag is en er op basis van deze gegevens geen uitspraak te doen is over een eventuele voorkeur voor een behandeling met DOAC's versus warfarine. Abi Mosleh (2023) voerde een retrospectieve studie uit naar postoperatieve complicaties, zoals bloedingen, in patiënten die een gastric bypass versus een gastric sleeve hebben ondergaan en preoperatief al een indicatie voor antistollingsbehandeling hadden. Ze rapporteren hierbij ook summiere gegevens over de verschillende antistollingsbehandelingen (DOACs en warfarine). Ook hiervoor geldt dat de bewijskracht gelimiteerd wordt door het risico op bias en ernstige imprecisie en er op basis van deze gegevens geen conclusie te trekken is over het effect van respectievelijk behandeling met DOAC versus warfarine.

Farmacodynamiek

Bariatrische chirurgie vermindert de absorptie van geneesmiddelen door het verstoren of omzeilen van het absorptieoppervlak van de proximale dunne darm, het veranderen van het metabolisme van geneesmiddelen door cytochroom P450 3A4 (CYP3A4) en p-glycoproteïne (p-gp) enzymen, het beperken van de calorie-inname, het veranderen van de intestinale transitie-tijden van geneesmiddelen en het veranderen van de oplosbaarheid van geneesmiddelen door veranderingen in de pH van de maag en darmen (Evers, 2017 en Padwal, 2010).

Apixaban wordt geabsorbeerd in de proximale dunne darm met beperkte absorptie in de maag en het colon (Eriksson, 2009 en Mueck, 2013). Rivaroxaban wordt geabsorbeerd in de maag met geleidelijke vermindering van de absorptie naarmate het geneesmiddel door de darm gaat (Mani, 2013). Dabigatran wordt geabsorbeerd in de maag en het duodenum (Martin, 2017) en edoxaban wordt voornamelijk geabsorbeerd in de proximale dunne darm (Mueck, 2013 en Parasrampuria, 2015). Absorptie van rivaroxaban en dabigatran kan worden beïnvloed door procedures die de maag verwijderen of omzeilen.

Plasmaspiegels

Het nut van het bepalen van plasmaspiegels als voorspeller voor de effectiviteit van DOAC's na bariatrische chirurgie is onzeker. Vanuit fase 3-studies, waarin DOAC's werden vergeleken met LMWH gevolgd door VKA, zijn geen vastgestelde referentiewaarden bekend voor top- en dalspiegels voor DOAC's, maar hoogstens streefwaarden (zie Tabel 1).

Tabel 2: Te verwachten top- en dalspiegels voor DOACs in patiënten behandeld in het kader van preventie van CVA of VTE. Vertaalde versie overgenomen uit Gosselin (2018).

	Dabigatran		**Rivaroxaban**		**Apixaban**		**Edoxaban**	
Indicatie	Preventie CVA bij NVAF	Behandeling PE/VTE	Preventie CVA bij NVAF	Behandeling PE/VTE	Preventie CVA bij NVAF	Behandeling PE/VTE	Preventie CVA bij NVAF	Behandeling PE/VTE
Dosering	150 mg 2dd	150 mg 2dd	20 mg 1dd	20 mg 1dd	5 mg 2dd	5 mg 2 dd	60 mg 1dd	60 mg 1 dd
Topspiegel (ng/mL)	175[a] (117-275)	175 [a] (117-275)	249[b] (184-343)	270 [b] (189-419)	171[c] (91-321)	132 [c] (59-302)	170[d] (125-245)	234[d] (149-317)

Dalspiegel (ng/mL)	91[a] (61-143)	60[a] (39-95)	44[b] (12-137)	26[b] (6-87)	103[c] (41-230)	63[c] (22-177)	36[e] (19-62)	19[e] (10-39)

CVA: cerebro vasculair accident, DD: daags, NVAF: Niet valvulair atriumfibrilleren, PE: pulmonale embolie, VTE: veneuze trombo-embolie. [a]: Gemiddelde (P25-P75), [b]: Gemiddelde (P5-P95), [c]: Mediaan (P5-P95), [d]: Mediaan (1.5*IQR), [e]: Mediaan (IQR)

Zowel de dalspiegel als de topspiegel kunnen een indicatie geven over de blootstelling aan een DOAC. De aanname is hierbij dat in het geval van te lage spiegels bij adequate inname het gebruik van deze DOAC afgeraden moet worden. Een topspiegel wordt drie uur na inname van de DOAC bepaald. Een dalspiegel (>48 uur gebruik van de DOAC) wordt 12 uur na inname van de DOAC bepaald bij een tweemaal daagse dosering (apixaban en dabigatran) en 24 uur na inname van de DOAC bij een eenmaal daagse dosering (rivaroxaban en edoxaban). Echter, de meeste studies na bariatrische chirurgie hebben tot nu toe topspiegels gebruikt. Vanuit de niet-bariatrische literatuur zijn er aanwijzingen dat dalspiegels ook gebruikt kunnen worden (van Edom, 2024; Gosselin, 2018; Sin, 2022). Dat is voor patiënten na bariatrische chirurgie niet onderzocht.

Ondanks de onzekerheid over de mate waarin plasmaspiegels een goede voorspeller zijn voor het voorkómen van recidieftrombose door een behandeling met DOAC's, worden de plasmaspiegels vaak gemeten om managementbeslissingen te nemen (Rottenstreich, 2018). Deze praktijk wordt ook onderschreven door internationale behandelrichtlijnen (Martin, 2021). Uit de zeer beperkte literatuur naar plasmaspiegels bij patiënten die bariatrische chirurgie ondergingen, komt naar voren dat bij alle patiënten die apixaban namen (N=13) de plasmaspiegels binnen de streefwaarden van de fase 2- en 3-studies waren, bij de patiënten op rivaroxaban (N=17) was dit bij ongeveer de helft van de patienten het geval, terwijl dit voor drie van de 12 patienten op dabigatran gold (Leong, 2022). In een andere studie werden bij patienten met morbide obesitas, die op apixaban of rivaroxaban stonden, anti-Xa topspiegels gemeten voorafgaand en na een Roux-en-Y bypass (RYGB) operatie. Preoperatieve analyses van plasma-anti-Xa-spiegels waren binnen het normale bereik bij zowel patiënten die apixaban gebruikten (N = 29; Body mass index (BMI) 44,5 ± 5,1 kg/m2) als patiënten die rivaroxaban gebruikten (N = 12; BMI 42,6 ± 5,9 kg/m2). Postoperatief waren de anti Xa-spiegels van apixaban allemaal binnen het therapeutische bereik, terwijl de anti-Xa-spiegels voor rivaroxaban subtherapeutisch waren in negen van de 14 (64%) patiënten. Perioperatieve longitudinale follow-up bij patiënten die apixaban gebruikten (n = 18) vertoonde geen significante verandering in anti-Xa-niveaus na RYGB. (Kok, 2022). In een kleine studie werden topspiegels gemeten bij patiënten die na een RYGB dabigatran gebruikten (Grainger, 2020). De mediane topspiegel was 34,6 ng/ml (range: 10-64 ng/ml), duidend op malabsorptie. Voor edoxaban zijn te weinig gegevens voorhanden.

Klinische praktijkervaringen

Hoewel er onvoldoende studies met klinische eindpunten voorhanden zijn, worden in Nederland al jarenlang veel patiënten die bariatrische chirurgie ondergingen en vooraf een indicatie voor een antistollingsbehandeling hadden, met name voor atriumfibrilleren, ook na bariatrische chirurgie met een DOAC behandeld. Hierbij gaat het specifiek om behandeling met rivaroxaban en apixaban, omdat bekend is dat bij het gebruik van dabigatran er een hoog risico is op te lage plasmaspiegels en er voor edoxaban te weinig gegevens zijn (Leong, 2022 en Grainger, 2020). In sommige centra worden daarbij ook systematisch spiegelbepalingen gedaan. Er is vanuit deze praktijk geen signaal gekomen dat trombotische complicaties vaker optreden bij de patiënten die verkozen hebben door te gaan met de DOAC-behandeling in plaats van het overgaan op een behandeling met vitamine K-antagonisten (VKA).

Het is relevant om rekening te houden met de indicatie voor de behandeling met een DOAC na bariatrische chirurgie, namelijk atriumfibrilleren, acute VTE of chronische behandeling na VTE. Bij een acute VTE gaat het zowel om patiënten die in aansluiting op de bariatrische chirurgie een VTE ontwikkelen alsook om patiënten die na een langere periode een VTE krijgen. Bij een acute VTE wordt de eerste week (apixaban) of drie weken (rivaroxaban) in een hogere dosis gegeven. Hiermee is weinig ervaring bij patiënten die bariatrische chirurgie hebben ondergaan. Daarom wordt vaak toch gekozen voor LMWH gedurende die eerste weken, gevolgd door een DOAC. Zo adviseren Martin et al (2017) om gedurende één maand LMWH te geven. In de chronische fase – zes maanden na een acute VTE - worden veel patiënten behandeld met een 50% dosis van apixaban of rivaroxaban. In verband met de onduidelijkheid over de opname en spiegels raden veel Nederlandse Bariatrische klinieken deze dosisreductie vooralsnog af bij patiënten die bariatrische chirurgie hebben ondergaan.

De adviezen voor patiënten die een indicatie voor antistolling ontwikkelen nadat zij bariatrische chirurgie hebben ondergaan zijn niet anders dan voor patiënten die preoperatief al een indicatie hadden. In beide situaties is het belangrijk dat de behandeling effectief is in het voorkómen van trombotische gebeurtenissen.

Naast de RYGB of de sleeve gastrectomie worden soms ook andere bariatrische operaties verricht, zoals *Omega-loop bypass* en de *Single anastomosis duodeno-ilial bypass*. Bij deze ingrepen ontstaat een verandering in de opname van voedsel en medicatie vergelijkbaar met de verandering na een RYGB. Echter, er zijn ook vormen van bariatrische chirurgie waarbij de lengte van de darm sterk gereduceerd wordt. Voorbeelden hiervan zijn de duodenal switch, de distale gastric bypass en de biliopancreatische diversie. Bij deze operaties ontstaat veel meer malabsorptie dan bij de RYGB en sleeve gastrectomie. In verband met veel meer twijfel over de opname van een DOAC, heeft behandeling met VKA in deze situaties de voorkeur.

Zolang patiënten moeite hebben met inname van tabletten of voedsel is het aan te raden geen DOAC's voor te schrijven. Er bestaat een te groot risico op onderbehandeling. Daarnaast is er een groep patiënten die na bariatrische chirurgie moeite heeft met *compliance*. Deze patiënten zijn onzorgvuldig met betrekking tot inname van de dagelijkse vitamines en supplementen, komen weinig bij follow-up controles en melden zich niet of laat bij complicaties. Bij deze groep patiënten heeft behandeling met VKA de voorkeur vanwege de INR controles, hoewel regulatie van VKA in deze groep ook moeizaam kan zijn.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>
De werkgroep kent geen onderzoek naar de waarden en voorkeuren van patiënten met betrekking tot antistollingsbehandeling na bariatrische chirurgie. Patiënten vinden het van belang om te worden voorgelicht over de beste wijze van behandelen waarbij duidelijk wordt gemaakt dat er een keuze is tussen een DOAC, waarbij apixaban of rivaroxaban de sterke voorkeur geniet, of VKA. Bij een DOAC dient bij aanvang van de behandeling de plasmaspiegels te worden bepaald ter controle van een goede opname uit het veranderde maagdarmkanaal. De dosering van de DOAC is dezelfde als bij patiënten zonder status na bariatrische chirurgie. Het is aannemelijk dat patiënten het belangrijk vinden dat de antistollingsbehandeling zowel effectief als veilig is. De onzekerheid die er bestaat ten aanzien van de voorspellende waarde van plasmaspiegels voor de blootstelling aan DOAC's dient daarom besproken te worden met de patiënt. Een eventuele overstap na een behandeling met VKA leidt tot meer monitoring en kan daarmee ook meer belastend zijn voor de patiënt. Ook dat dient meegenomen te worden in het gesprek. Tot slot is er een deel

van de patiënten die moeite heeft met de zogenaamde compliance. Voor deze patiënten geldt dat het mogelijk beter is om over te stappen naar een behandeling met een VKA.

Kosten (middelenbeslag)

Overwegingen met betrekking tot kosten spelen geen doorslaggevende rol in het opstellen van de aanbeveling. De kosten die gepaard gaan met een DOAC-behandeling zijn lager dan die van een behandeling met VKA.

Aanvaardbaarheid, haalbaarheid en implementatie

Er bestaat onzekerheid over de effectiviteit van antistolling na bariatrische chirurgie. Toch worden al jarenlang veel mensen na bariatrische chirurgie met DOACs behandeld zonder dat er een signaal is van meer trombotische complicaties. Met deze ervaring en omdat de aanbeveling is om deze onzekerheid eerst met patiënten te bespreken, is te verwachten dat artsen in Nederland geen grote bezwaren tegen de voorgestelde aanbevelingen zullen hebben. Als vanwege lage gezondheidsvaardigheden of een taalbarrière geen goede counseling en samen beslissen mogelijk is, kan voor VKA gekozen worden.
Belemmerende factor bij de haalbaarheid van implementatie kan het meten van spiegels zijn. Dat is niet bij alle priklocaties van de laboratoria mogelijk. Ook vergt het extra tijd en inspanning om de gesprekken over keuze van antistolling te voeren, niet alleen initieel, maar ook tijdens de follow-up bij chronische behandeling.

Aanbeveling

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Het is redelijk om bij patiënten, die bariatrische chirurgie hebben ondergaan en preoperatief al een indicatie voor antistolling hadden, een initiële periode van ten minimale 48 uur met parenterale antistolling therapeutische doses LMWH te geven, vanwege de initiële postoperatieve fase. Hierna is het redelijk om met een FXa-remmer (apixaban boven rivaroxaban of edoxaban) te starten. Apixaban is het middel van voorkeur. Argumenten om een DOAC (FXa-remmer) te kiezen zijn het gebruikersgemak (niet doordoseren, geen INR-metingen) en een lager risico op intracraniële bloedingen. Argumenten tegen het gebruik van een DOAC (FXa-remmer) zijn dat er onzekerheid is over de absorptie en de waarde van spiegelmetingen (anti-Xa), terwijl bij een behandeling met een VKA de dosering op basis van INR-metingen aangepast kan worden. Argumenten om met apixaban te starten boven rivaroxaban zijn afgeleid uit de literatuur waarbij bleek dat de spiegels van apixaban bij patiënten na bariatrische chirurgie van voldoende niveau waren of bleven terwijl dit bij rivaroxaban minder het geval was. Voor edoxaban zijn te weinig gegevens voorhanden. Hierbij wordt aangeraden om een DOAC-dalspiegel of -topspiegel te meten. Een dalspiegel wordt 12 uur na de ochtenddosis bij tweemaal daagse doseringen 24 uur na de eenmaal daagse dosering afgenomen, in beide gevallen vlak voor de volgende dosering. Een topspiegel wordt drie uur na inname afgenomen. Vervolgens wordt een geneesmiddel specifieke chromogene anti-Xa bepaling verricht en deze spiegel wordt vergeleken met de verwachte top- of dalspiegels volgens de literatuur. De timing van de lab-afname voor dalspiegels is wat eenvoudiger dan voor een topspiegel en bij een dalspiegel bestaat niet de onzekerheid over wanneer DOAC de topspiegel bereikt. Het is aan te raden om de onzekerheid van de therapeutische spiegels en het ontbreken van goede literatuur met betrekking tot klinisch relevante uitkomsten met de patiënt te bespreken en samen tot een passende behandeling te komen.

Geef patiënten die bariatrische chirurgie (gastric sleeve of gastric bypass) hebben ondergaan en vooraf een indicatie voor antistolling hadden, vanaf tenminste 48 uur

postoperatief een parenteraal antistollingsmiddel (LMWH of fondaparinux) voor een minimale periode van 48 uur.

Patiënten met atriumfibrilleren of chronische behandeling voor VTE
Bespreek met de patiënt de voor- en nadelen van het (her)starten van de antistollingsbehandeling met respectievelijk DOAC of VKA, de onzekerheden die er zijn over de opname van de middelen en het ontbreken van literatuur over klinisch relevante uitkomsten. Maak samen met de patiënt de keuze om de behandeling met DOAC of VKA te (her)starten.

Patiënten met een acute VTE na bariatrische chirurgie
Geef initieel LMWH gedurende 1 maand. Dit kan gevolgd worden door DOAC of VKA. Bespreek met de patiënt de voor- en nadelen van het starten van de antistollingsbehandeling met respectievelijk DOAC of VKA, de onzekerheden die er zijn over de opname van de middelen en het ontbreken van literatuur over klinisch relevante uitkomsten. Maak samen met de patiënt de keuze om de behandeling met DOAC of VKA te starten.

Als gekozen wordt om DOAC te (her)starten:

- Schrijf een behandeling met apixaban (eerste keuze) of rivaroxaban (tweede keuze) voor;
- Overweeg om plasmaspiegels te bepalen ter controle van de opname van een DOAC. Hierbij kan worden gekozen voor top- of dalspiegels;
- Overweeg om geen dosisreductie van een DOAC te geven voor secundaire preventie van VTE na bariatrische chirurgie, aangezien deze dosisreductie niet is onderzocht in deze populatie.

Kennisvragen

Wat is het effect van aanpassing in DOAC-therapie (naar andere DOAC of VKA), vergeleken met standaardzorg (geen aanpassing in de DOAC-therapie), in patiënten die bariatrische chirurgie hebben ondergaan en preoperatief een indicatie hadden voor een therapeutische dosis DOAC's?

Wat is het effect van dosisreductie naar 50% na meer dan zes maanden behandeling bij patiënten die bariatrische chirurgie hebben ondergaan?.

Hierbij wil de werkgroep graag benoemen dat voor de behandeling met dabigatran bekend is dat het risico op lage plasmaspiegels erg hoog is bij patiënten die bariatrische chirurgie hebben ondergaan. Daarmee lijkt het niet ethisch om dabigatran in deze patiëntengroep te onderzoeken en zal de focus moeten liggen op FXa-remmers.

Daarnaast zijn het verder valideren van dal- en topspiegels voor de dagelijkse praktijk en het correleren van farmacokinetische parameters met klinische uitkomsten belangrijke kennisvragen.

Literatuur

Abi Mosleh K, Belluzzi A, Salame M, Kendrick ML, Abu Dayyeh BK, McKenzie TJ, Ghanem OM. Long-Term Outcomes of Bariatric Surgery in Patients on Chronic Anticoagulation. Obes Surg. 2023 Dec;33(12):4007-4016. doi: 10.1007/s11695-023-06910-x. Epub 2023 Nov 2. PMID: 37917392.

Van Edom CJ, Cools B, Droogné W, Jacobs S, Van Puyvelde J, Vlasselaers D, Vanassche T, Meyns B. Apixaban plasma levels in patients with HeartMate 3 support. J Heart

Lung Transplant. 2024 Nov 15:S1053-2498(24)01940-5. doi: 10.1016/j.healun.2024.11.003. Epub ahead of print. PMID: 39551171.

Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor xa inhibitors in development. Clin Pharmacokinet. 2009;48(1):1-22. doi: 10.2165/0003088-200948010-00001. PMID: 19071881.

Evers SS, Sandoval DA, Seeley RJ. The Physiology and Molecular Underpinnings of the Effects of Bariatric Surgery on Obesity and Diabetes. Annu Rev Physiol. 2017 Feb 10;79:313-334. doi: 10.1146/annurev-physiol-022516-034423. Epub 2016 Nov 28. PMID: 27912678.

Gosselin RC, Adcock DM, Bates SM, Douxfils J, Favaloro EJ, Gouin-Thibault I, Guillermo C, Kawai Y, Lindhoff-Last E, Kitchen S. International Council for Standardization in Haematology (ICSH) Recommendations for Laboratory Measurement of Direct Oral Anticoagulants. Thromb Haemost. 2018 Mar;118(3):437-450. doi: 10.1055/s-0038-1627480. Epub 2018 Feb 12. PMID: 29433148.

Grainger B, Holloway R, Merriman E, Booth M, Royle G, Babor R, Beban G, Young L. Evidence of impaired dabigatran absorption following laparoscopic Roux-en-Y gastric bypass surgery: the Auckland regional experience (2011-2018). Br J Haematol. 2020 Oct;191(2):e67-e69. doi: 10.1111/bjh.17004. Epub 2020 Jul 28. PMID: 32720718.

Hendricks AK, Zieminski JJ, Yao X, Dunlay SM, Sangaralingham LR, O'Meara JG, Herrin TR, Nei SD. Safety and Efficacy of Oral Anticoagulants for Atrial Fibrillation in Patients After Bariatric Surgery. Am J Cardiol. 2020 Dec 1;136:76-80. doi: 10.1016/j.amjcard.2020.09.020. Epub 2020 Sep 15. PMID: 32941819.

Kok T, de Boer H, Witteman B, Hovens M, van Luin M, Monajemi H. Anti-Xa Levels in Morbidly Obese Patients Using Apixaban or Rivaroxaban, Before and After Bariatric Surgery. Obes Surg. 2022 Mar;32(3):607-614. doi: 10.1007/s11695-021-05814-y. Epub 2021 Nov 25. PMID: 34822108.

Leong R, Chu DK, Crowther MA, Mithoowani S. Direct oral anticoagulants after bariatric surgery-What is the evidence? J Thromb Haemost. 2022 Sep;20(9):1988-2000. doi: 10.1111/jth.15823. Epub 2022 Jul 28. PMID: 35844166.

Mani H, Kasper A, Lindhoff-Last E. Measuring the anticoagulant effects of target specific oral anticoagulants-reasons, methods and current limitations. J Thromb Thrombolysis. 2013 Aug;36(2):187-94. doi: 10.1007/s11239-013-0907-y. PMID: 23512159.

Martin KA, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. J Thromb Haemost. 2021 Aug;19(8):1874-1882. doi: 10.1111/jth.15358. Epub 2021 Jul 14. PMID: 34259389.

Martin KA, Lee CR, Farrell TM, Moll S. Oral Anticoagulant Use After Bariatric Surgery: A Literature Review and Clinical Guidance. Am J Med. 2017 May;130(5):517-524. doi: 10.1016/j.amjmed.2016.12.033. Epub 2017 Feb 1. PMID: 28159600; PMCID: PMC5401640.

Mueck W, Schwers S, Stampfuss J. Rivaroxaban and other novel oral anticoagulants: pharmacokinetics in healthy subjects, specific patient populations and relevance of coagulation monitoring. Thromb J. 2013 Jun 28;11(1):10. doi: 10.1186/1477-9560-11-10. PMID: 23809871; PMCID: PMC3726366.

Padwal R, Brocks D, Sharma AM. A systematic review of drug absorption following bariatric surgery and its theoretical implications. Obes Rev. 2010 Jan;11(1):41-50. doi: 10.1111/j.1467-789X.2009.00614.x. Epub 2009 Jun 2. PMID: 19493300.

Parasrampuria DA, Kanamaru T, Connor A, Wilding I, Ogata K, Shimoto Y, Kunitada S. Evaluation of regional gastrointestinal absorption of edoxaban using the enterion capsule. J

Clin Pharmacol. 2015 Nov;55(11):1286-92. doi: 10.1002/jcph.540. Epub 2015 Jun 26. PMID: 25969414; PMCID: PMC4755158.

Rottenstreich A, Barkai A, Arad A, Raccah BH, Kalish Y. The effect of bariatric surgery on direct-acting oral anticoagulant drug levels. Thromb Res. 2018 Mar;163:190-195. doi: 10.1016/j.thromres.2017.11.006. Epub 2017 Nov 15. PMID: 29157916.

Sin CF, Wong KP, Wong TF, Siu CW, Yap DYH. Plasma apixaban levels in Chinese patients with chronic kidney disease-Relationship with renal function and bleeding complications. Front Pharmacol. 2022 Dec 8;13:928401. doi: 10.3389/fphar.2022.928401. PMID: 36569289; PMCID: PMC9772439.

Srivastava K, Patel N, Tabbara M, Liew A, Zaghloul I, Migliore MM, Mekary RA. Thromboembolism, Bleeding, and Mortality Incidence of Direct Oral Anticoagulants Versus Warfarin Postbariatric Surgery. Am J Med. 2021 Nov;134(11):1403-1412.e2. doi: 10.1016/j.amjmed.2021.06.021. Epub 2021 Jul 14. PMID: 34273283.

Bijlagen bij module bariatrische chirurgie

Implementatieplan

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijke kennisvraag
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	**Sterkte van de aanbeveling**	**Bewijskracht per uitkomstmaat**	**Verkeerslicht per (sub)aanbeveling**
Geef patiënten die bariatrische chirurgie (gastric sleeve of gastric bypass) hebben ondergaan en vooraf een indicatie voor antistolling hadden, vanaf tenminste 48 uur postoperatief een parenteraal antistollingsmiddel (LMWH of fondaparinux) voor een minimale periode van 48 uur. ***Patiënten met atriumfibrilleren of chronische behandeling voor VTE***	□ Sterk (doe/ gebruik) / **X** Zwak (overweeg)	Overall bewijskracht □ **H** □ **M** □ **L** □ **VL** **X NG** **Range bewijskracht van alle uitkomstmaten** □ **H** □ **M** □ **L** □ **VL** **X NG** **OF** □ **voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in **X ORANJE:** gebruik tabel B □ **LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in

Bespreek met de patiënt de voor- en nadelen van het (her)starten van de antistollingsbehandeling met respectievelijk DOAC of VKA, de onzekerheden die er zijn over de opname van de middelen en het ontbreken van literatuur over klinisch relevante uitkomsten. Maak samen met de patiënt de keuze om de behandeling met DOAC of VKA te (her)starten. ***Patiënten met een acute VTE na bariatrische chirurgie*** Geef initieel LMWH gedurende 1 maand. Dit kan gevolgd worden door DOAC of VKA. Bespreek met de patiënt de voor- en nadelen van het starten van de antistollingsbehandeling met respectievelijk DOAC of VKA, de onzekerheden die er zijn over de opname van de middelen en het ontbreken van literatuur over klinisch relevante uitkomsten. Maak samen met de patiënt de keuze om de behandeling met DOAC of VKA te starten. ***Als gekozen wordt om DOAC te (her)starten:*** • Schrijf een behandeling met apixaban (eerste keuze) of rivaroxaban (tweede keuze) voor; • Overweeg om plasmaspiegels te bepalen ter controle van de opname van een DOAC. Hierbij kan worden gekozen voor			

top- of dalspiegels; • Overweeg om geen dosisreductie van een DOAC te geven voor secundaire preventie van VTE na bariatrische chirurgie, aangezien deze dosisreductie niet is onderzocht in deze populatie.			

Implementatietabel

Aanbeveling Geef patiënten die bariatrische chirurgie (gastric sleeve of gastric bypass) hebben ondergaan en vooraf een indicatie voor antistolling hadden, vanaf tenminste 48 uur postoperatief een parenteraal antistollingsmiddel (LMWH of fondaparinux) voor een minimale periode van 48 uur. ***Patiënten met atriumfibrilleren of chronische behandeling voor VTE*** Bespreek met de patiënt de voor- en nadelen van het (her)starten van de antistollingsbehandeling met respectievelijk DOAC of VKA, de onzekerheden die er zijn over de opname van de middelen en het ontbreken van literatuur over klinisch relevante uitkomsten. Maak samen met de patiënt de keuze om de behandeling met DOAC of VKA te (her)starten. ***Patiënten met een acute VTE na bariatrische chirurgie*** Geef initieel LMWH gedurende 1 maand. Dit kan	Op basis van de beschikbare evidentie en ervaring uit de praktijk kon er onvoldoende richting aan de besluitvorming worden gegeven. Om die reden is er geen beschrijving van belemmeringen en kansen voor implementatie van de aanbeveling toegevoegd. Disseminatie van de kennis in deze module verloopt via de standaard route. De module wordt gepubliceerd op de Richtlijnendatabase.

gevolgd worden door DOAC of VKA. Bespreek met de patiënt de voor- en nadelen van het starten van de antistollingsbehandeling met respectievelijk DOAC of VKA, de onzekerheden die er zijn over de opname van de middelen en het ontbreken van literatuur over klinisch relevante uitkomsten. Maak samen met de patiënt de keuze om de behandeling met DOAC of VKA te starten. ***Als gekozen wordt om DOAC te (her)starten:*** • Schrijf een behandeling met apixaban (eerste keuze) of rivaroxaban (tweede keuze) voor; • Overweeg om plasmaspiegels te bepalen ter controle van de opname van een DOAC. Hierbij kan worden gekozen voor top- of dalspiegels; • Overweeg om geen dosisreductie van een DOAC te geven voor secundaire preventie van VTE na bariatrische chirurgie, aangezien deze dosisreductie niet is onderzocht in deze populatie.	

Evidence tables
Not applicable

5 Table of excluded studies

Reference	Reason for exclusion
Kröll D, Nett PC, Borbély YM, Schädelin S, Bertaggia Calderara D, Alberio L, Stirnimann G. The effect of bariatric surgery on the direct oral anticoagulant rivaroxaban: the extension study. Surg Obes Relat Dis. 2018 Dec;14(12):1890-1896. doi: 10.1016/j.soard.2018.08.025. Epub 2018 Sep 19. PMID: 30396779.	Wrong comparison (2 surgical procedures, pre- and postoperative)

Hanarz M, Gołąb A, Plicner D, Undas A. Direct oral anticoagulants in patients with atrial fibrillation following bariatric surgery: A single center experience. Kardiol Pol. 2021;79(12):1378-1381. doi: 10.33963/KP.a2021.0165. Epub 2021 Dec 2. PMID: 34856633.	Wrong publication type (short communication)
Nasser MF, Jabri A, Gandhi S, Rader F. Oral Anticoagulant Use in Morbid Obesity and Post Bariatric Surgery: A Review. Am J Med. 2021 Dec;134(12):1465-1475. doi: 10.1016/j.amjmed.2021.07.017. Epub 2021 Aug 15. PMID: 34403701.	Narrative review
Hendricks AK, Zieminski JJ, Yao X, Dunlay SM, Sangaralingham LR, O'Meara JG, Herrin TR, Nei SD. Safety and Efficacy of Oral Anticoagulants for Atrial Fibrillation in Patients After Bariatric Surgery. Am J Cardiol. 2020 Dec 1;136:76-80. doi: 10.1016/j.amjcard.2020.09.020. Epub 2020 Sep 15. PMID: 32941819.	Wrong comparison (DOAC vs warfarin), included patients that developed indication for anticoagulation after bariatric surgery
Leong R, Chu DK, Crowther MA, Mithoowani S. Direct oral anticoagulants after bariatric surgery-What is the evidence? J Thromb Haemost. 2022 Sep;20(9):1988-2000. doi: 10.1111/jth.15823. Epub 2022 Jul 28. PMID: 35844166.	Wrong inclusion criteria (included case series, case reports and abstracts; included three cohort studies of which one was Hendricks, 2020 and others did not fulfil inclusion criteria (abstract or wrong comparison (bariatric surgery vs control)
Srivastava K, Patel N, Tabbara M, Liew A, Zaghloul I, Migliore MM, Mekary RA. Thromboembolism, Bleeding, and Mortality Incidence of Direct Oral Anticoagulants Versus Warfarin Post bariatric Surgery. Am J Med. 2021 Nov;134(11):1403-1412.e2. doi: 10.1016/j.amjmed.2021.06.021. Epub 2021 Jul 14. PMID: 34273283.	Wrong study design (compared pooled results on DOAC and pooled results warfarin, no head to head comparisons available), not clear whether patients already used DOACs preoperatively
Martin KA, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. J Thromb Haemost. 2021 Aug;19(8):1874-1882. doi: 10.1111/jth.15358. Epub 2021 Jul 14. PMID: 34259389.	Wrong publication type (guidelines)
Abi Mosleh K, Belluzzi A, Salame M, Kendrick ML, Abu Dayyeh BK, McKenzie TJ, Ghanem OM. Long-Term Outcomes of Bariatric Surgery in Patients on Chronic Anticoagulation. Obes Surg. 2023 Dec;33(12):4007-4016. doi: 10.1007/s11695-023-06910-x. Epub 2023 Nov 2. PMID: 37917392.	Focus on comparison between RGYB and SG. Data on DOAC vs warfarin postoperatievely is too limited (no baseline characteristics etc)

Literature search strategy

Zoekverantwoording

Algemene informatie

Cluster/richtlijn: Antitrombotisch beleid - UV9 Antistollingsbeleid na bariatrische chirurgie	
Uitgangsvraag/modules: Wat is de optimale therapeutische antistollingsbehandeling bij patiënten die bariatrische chirurgie hebben ondergaan?	
Database(s): Embase.com, Ovid/Medline	Datum: 21 augustus 2024
Periode: vanaf 2000	Talen: geen restrictie
Literatuurspecialist: Esther van der Bijl	

BMI-zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Deduplication: voor het ontdubbelen is gebruik gemaakt van http://dedupendnote.nl/
Toelichting: Voor deze vraag is gezocht op de elementen bariatrische chirurgie EN antistollingsbehandeling. De sleutelartikelen worden gevonden met deze search. Zoals afgesproken worden de resultaten in een set aangeboden voor AS Review.

Zoekopbrengst 21 augustus 2024

	EMBASE	OVID/MEDLINE	Ontdubbeld
SR	199	55	
RCT	432	101	
Observationele studies	643	209	
Totaal	1274	365	**1361***

voor AS Review

5 ***Zoekstrategie Embase.com 21 augustus 2024***

No.	Query	Results
#1	'bariatric surgery'/exp OR 'biliopancreatic bypass'/exp OR 'biliopancreatic diversion with duodenal switch'/exp OR 'single anastomosis duodeno-ileal bypass with sleeve gastrectomy'/exp OR 'gastric banding'/exp OR 'gastric bypass surgery'/exp OR 'roux-en-y gastric bypass'/exp OR 'sleeve gastrectomy'/exp OR (((bariatric* OR obesit* OR 'weight loss*' OR 'weight reduction*' OR 'gastric sleeve*') NEAR/3 (operation* OR procedure* OR surger* OR surgic*)):ti,ab,kw) OR (((biliopancreatic OR 'bilio pancreatic' OR pancreatobiliar*) NEAR/3 (bypass* OR diversion*)):ti,ab,kw) OR ((('duodeno-ileal' OR 'duodenal ileostom*' OR 'duodeno ileostom*' OR duodenoileal OR 'post pyloric') NEAR/3 (bypass* OR anastomosis OR gastrectom*)):ti,ab,kw) OR (((stomach OR gastric OR gastroileal) NEAR/3 (banding* OR bypass*)):ti,ab,kw) OR ((sleeve* NEAR/3 gastrectom*):ti,ab,kw) OR scopinaro*:ti,ab,kw OR 'bpd ds':ti,ab,kw OR 'duodenal switch*':ti,ab,kw OR 'sadi s':ti,ab,kw OR 'roux-en-y':ti,ab,kw OR 'stomach stapling*':ti,ab,kw OR gastroenterostom*:ti,ab,kw OR 'gastro enterostom*':ti,ab,kw OR gastrojejunostom*:ti,ab,kw OR 'gastro jejunostom*':ti,ab,kw OR gastroplast*:ti,ab,kw	100843
#2	'thrombosis prevention'/exp OR 'anticoagulant agent'/exp OR 'anticoagulation'/exp OR 'anticoagulant therapy'/exp OR thromboprophyla*:ti,ab,kw OR ((thrombo* NEAR/3 (prophylaxis OR prophylactic OR prevention)):ti,ab,kw) OR 'anti coagulant*':ti,ab,kw OR 'anticoagulant*':ti,ab,kw OR 'anticoagulat*':ti,ab,kw OR 'anti coagulat*':ti,ab,kw OR 'antithrombotic*':ti,ab,kw OR 'anti	946238

	thrombotic*':ti,ab,kw OR 'antithrombocytic*':ti,ab,kw OR 'anti thrombocytic*':ti,ab,kw OR 'antiplatelet agent*':ti,ab,kw OR 'antiplatelet drug*':ti,ab,kw OR 'platelet aggregation inhibitor*':ti,ab,kw OR 'platelet inhibitor*':ti,ab,kw OR 'platelet antagonist*':ti,ab,kw OR 'thrombocyte aggregation inhibiting agent*':ti,ab,kw OR 'thrombocyte aggregation inhibitor*':ti,ab,kw OR 'direct oral anticoagulant agent'/exp OR 'direct oral anticoagulant'/exp OR doac*:ti,ab,kw OR 'apixaban'/exp OR 'aboxoma':ti,ab,kw OR 'apixaban':ti,ab,kw OR 'apixaben':ti,ab,kw OR 'bms 562247':ti,ab,kw OR 'bms562247':ti,ab,kw OR 'eliques':ti,ab,kw OR 'eliquis':ti,ab,kw OR 'lunast':ti,ab,kw OR 'pf 0465257':ti,ab,kw OR 'pf0465257':ti,ab,kw OR 'tah 3311':ti,ab,kw OR 'tah 3341':ti,ab,kw OR 'tah3311':ti,ab,kw OR 'tah3341':ti,ab,kw OR 'dabigatran'/exp OR 'bibr 953':ti,ab,kw OR 'bibr953':ti,ab,kw OR 'dabigatran':ti,ab,kw OR 'edoxaban'/exp OR 'du 176':ti,ab,kw OR 'du 176b':ti,ab,kw OR 'du176':ti,ab,kw OR 'du176b':ti,ab,kw OR 'edoxaban':ti,ab,kw OR 'endoxaban':ti,ab,kw OR 'lixiana':ti,ab,kw OR 'roteas':ti,ab,kw OR 'savaysa':ti,ab,kw OR 'rivaroxaban'/exp OR 'assubex':ti,ab,kw OR 'ast 8294':ti,ab,kw OR 'ast8294':ti,ab,kw OR 'bay 59 7939':ti,ab,kw OR 'bay 597939':ti,ab,kw OR 'bay59 7939':ti,ab,kw OR 'bay597939':ti,ab,kw OR 'bs 112':ti,ab,kw OR 'bs112':ti,ab,kw OR 'dst 8294':ti,ab,kw OR 'dst8294':ti,ab,kw OR 'jnj 39039039':ti,ab,kw OR 'jnj39039039':ti,ab,kw OR 'kriva':ti,ab,kw OR 'naxat':ti,ab,kw OR 'rivaro':ti,ab,kw OR 'rivarolto':ti,ab,kw OR 'rivaroxaban':ti,ab,kw OR 'rivaxa':ti,ab,kw OR 'throsaben':ti,ab,kw OR 'xanirva':ti,ab,kw OR 'xarelto':ti,ab,kw OR 'xerdoxo':ti,ab,kw OR 'xindus':ti,ab,kw OR 'antivitamin k'/exp OR 'anti vitamin k':ti,ab,kw OR 'antivitamin k':ti,ab,kw OR 'antivitamins k':ti,ab,kw OR 'vitamin k antagonist':ti,ab,kw OR vka:ti,ab,kw OR 'warfarin'/exp OR 'acetonylbenzylhydroxycoumarin':ti,ab,kw OR 'adoisine':ti,ab,kw OR 'aldocumar':ti,ab,kw OR 'antrombin k':ti,ab,kw OR 'athrombin':ti,ab,kw OR 'athrombin k':ti,ab,kw OR 'athrombine k':ti,ab,kw OR 'athrombinek':ti,ab,kw OR 'befarin':ti,ab,kw OR 'bms 565793':ti,ab,kw OR 'bms565793':ti,ab,kw OR 'carfin':ti,ab,kw OR 'circuvit':ti,ab,kw OR 'compound 42':ti,ab,kw OR 'coumadan':ti,ab,kw OR 'coumadan sodico':ti,ab,kw OR 'coumadin':ti,ab,kw OR 'coumadine':ti,ab,kw OR 'coumafene':ti,ab,kw OR 'coumaphene':ti,ab,kw OR 'dagonal':ti,ab,kw OR 'farin':ti,ab,kw OR 'jantoven':ti,ab,kw OR 'kumatox':ti,ab,kw OR 'maforan':ti,ab,kw OR 'marevan':ti,ab,kw OR 'marfarin':ti,ab,kw OR 'martefarin':ti,ab,kw OR 'orfarin':ti,ab,kw OR 'panwarfarin':ti,ab,kw OR 'panwarfin':ti,ab,kw OR 'prothromadin':ti,ab,kw OR 'simarc-2':ti,ab,kw OR 'sodium warfarinum':ti,ab,kw OR 'sofarin':ti,ab,kw OR 'tintorane':ti,ab,kw OR 'uniwarfin':ti,ab,kw OR 'wafarin':ti,ab,kw OR 'waran':ti,ab,kw OR 'warf compound 42':ti,ab,kw OR 'warfant':ti,ab,kw OR 'warfar':ti,ab,kw OR 'warfarin':ti,ab,kw OR 'warfarine':ti,ab,kw OR 'warfarinum sodium':ti,ab,kw OR 'warfil 5':ti,ab,kw OR 'warfilone':ti,ab,kw OR 'warfin':ti,ab,kw OR 'warnerin':ti,ab,kw	

#3	#1 AND #2	2884
#4	#3 AND [2000-2024]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	2024
#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	1054862
#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	4091782
#7	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	8369973
#8	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR	15328565

	arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR (('or' OR 'rr') NEAR/6 ci):ab)))	
#9	#4 AND #5 – SR's	199
#10	#4 AND #6 NOT #9 – RCT's	432
#11	#4 AND (#7 OR #8) NOT (#9 OR #10) – Observationeel	643
#12	#9 OR #10 OR #11	1274

Zoekstrategie Ovid/Medline 21 augustus 2024

#	Searches	Results
1	exp Bariatric Surgery/ or exp Gastric Bypass/ or exp Gastric Bypass/ or exp Gastroplasty/ or exp Jejunoileal Bypass/ or ((bariatric* or obesit* or weight loss* or weight reduction* or gastric sleeve*) adj3 (operation* or procedure* or surger* or surgic*)).ti,ab,kf. or ((biliopancreatic or bilio pancreatic or pancreatobiliar*) adj3 (bypass* or diversion*)).ti,ab,kf. or ((duodeno-ileal or duodenal ileostom* or duodeno ileostom* or duodenoileal or post pyloric) adj3 (bypass* or anastomosis or gastrectom*)).ti,ab,kf. or ((stomach or gastric or gastroileal) adj3 (banding* or bypass*)).ti,ab,kf. or (sleeve* adj3 gastrectom*).ti,ab,kf. or scopinaro*.ti,ab,kf. or bpd ds.ti,ab,kf. or duodenal switch*.ti,ab,kf. or sadi s.ti,ab,kf. or roux-en-y.ti,ab,kf. or stomach stapling*.ti,ab,kf. or gastroenterostom*.ti,ab,kf. or gastro enterostom*.ti,ab,kf. or gastrojejunostom*.ti,ab,kf. or gastro jejunostom*.ti,ab,kf. or gastroplast*.ti,ab,kf.	59691
2	exp Anticoagulants/ or exp Platelet Aggregation Inhibitors/ or thromboprophyla*.ti,ab,kf. or (thrombo* adj3 (prophylaxis or	464987

	prophylactic or prevention)).ti,ab,kf. or (anti coagulant* or anticoagulant* or anticoagulat* or anti coagulat* or antithrombotic* or anti thrombotic* or antithrombocytic* or anti thrombocytic* or 'antiplatelet agent*' or 'antiplatelet drug*' or 'platelet aggregation inhibitor*' or 'platelet inhibitor*' or platelet antagonist* or 'thrombocyte aggregation inhibiting agent*' or 'thrombocyte aggregation inhibitor*' or doac*).ti,ab,kf. or aboxoma.ti,ab,kf. or apixaban.ti,ab,kf. or apixaben.ti,ab,kf. or bms 562247.ti,ab,kf. or bms562247.ti,ab,kf. or eliques.ti,ab,kf. or eliquis.ti,ab,kf. or lunast.ti,ab,kf. or "pf 0465257".ti,ab,kf. or pf0465257.ti,ab,kf. or tah 3311.ti,ab,kf. or tah 3341.ti,ab,kf. or tah3311.ti,ab,kf. or tah3341.ti,ab,kf. or exp Dabigatran/ or bibr 953.ti,ab,kf. or bibr953.ti,ab,kf. or dabigatran.ti,ab,kf. or du 176.ti,ab,kf. or du 176b.ti,ab,kf. or du176.ti,ab,kf. or du176b.ti,ab,kf. or edoxaban.ti,ab,kf. or endoxaban.ti,ab,kf. or lixiana.ti,ab,kf. or roteas.ti,ab,kf. or savaysa.ti,ab,kf. or exp Rivaroxaban/ or assubex.ti,ab,kf. or ast 8294.ti,ab,kf. or ast8294.ti,ab,kf. or bay 59 7939.ti,ab,kf. or bay 597939.ti,ab,kf. or bay59 7939.ti,ab,kf. or bay597939.ti,ab,kf. or bs 112.ti,ab,kf. or bs112.ti,ab,kf. or dst 8294.ti,ab,kf. or dst8294.ti,ab,kf. or jnj 39039039.ti,ab,kf. or jnj39039039.ti,ab,kf. or kriva.ti,ab,kf. or naxat.ti,ab,kf. or rivaro.ti,ab,kf. or rivarolto.ti,ab,kf. or rivaroxaban.ti,ab,kf. or rivaxa.ti,ab,kf. or throsaben.ti,ab,kf. or xanirva.ti,ab,kf. or xarelto.ti,ab,kf. or xerdoxo.ti,ab,kf. or xindus.ti,ab,kf. or exp Vitamin K/ or anti vitamin k.ti,ab,kf. or antivitamin k.ti,ab,kf. or antivitamins k.ti,ab,kf. or vitamin k antagonist.ti,ab,kf. or vka.ti,ab,kf. or exp Warfarin/ or acetonylbenzylhydroxycoumarin.ti,ab,kf. or adoisine.ti,ab,kf. or aldocumar.ti,ab,kf. or antrombin k.ti,ab,kf. or athrombin.ti,ab,kf. or athrombin k.ti,ab,kf. or athrombine k.ti,ab,kf. or athrombinek.ti,ab,kf. or befarin.ti,ab,kf. or bms 565793.ti,ab,kf. or bms565793.ti,ab,kf. or carfin.ti,ab,kf. or circuvit.ti,ab,kf. or compound 42.ti,ab,kf. or coumadan.ti,ab,kf. or coumadan sodico.ti,ab,kf. or coumadin.ti,ab,kf. or coumadine.ti,ab,kf. or coumafene.ti,ab,kf. or coumaphene.ti,ab,kf. or dagonal.ti,ab,kf. or farin.ti,ab,kf. or jantoven.ti,ab,kf. or kumatox.ti,ab,kf. or maforan.ti,ab,kf. or marevan.ti,ab,kf. or marfarin.ti,ab,kf. or martefarin.ti,ab,kf. or orfarin.ti,ab,kf. or panwarfarin.ti,ab,kf. or panwarfin.ti,ab,kf. or prothromadin.ti,ab,kf. or simarc-2.ti,ab,kf. or sodium warfarinum.ti,ab,kf. or sofarin.ti,ab,kf. or tintorane.ti,ab,kf. or uniwarfin.ti,ab,kf. or wafarin.ti,ab,kf. or waran.ti,ab,kf. or warf compound 42.ti,ab,kf. or warfant.ti,ab,kf. or warfar.ti,ab,kf. or warfarin.ti,ab,kf. or warfarine.ti,ab,kf. or warfarinum sodium.ti,ab,kf. or warfil 5.ti,ab,kf. or warfilone.ti,ab,kf. or warfin.ti,ab,kf. or warnerin.ti,ab,kf.	
3	1 and 2	693
4	limit 3 to yr="2000 -Current"	655
5	4 not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)	610

6	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	768920
7	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2766837
8	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4806846
9	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or	5765434

	'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	
10	5 and 6 – SR's	55
11	(5 and 7) not 10 – RCT's	101
12	(5 and (8 or 9)) not (10 or 11) – Observationeel	209
13	10 or 11 or 12	365

5

Module 8 Antitrombotisch beleid bij endoscopische ingrepen

Autorisatie en geldigheid

Autorisatiedatum:	*pending*
Eerstvolgende beoordeling actualiteit	volgende cyclus binnen het cluster Antitrombotisch beleid
Geautoriseerd door:	*pending*
Belangrijkste wijzigingen t.o.v. vorige versie:	n.v.t., het betreft een nieuwe module
Herbevestiging:	n.v.t.
Regiehouder:	Nederlandse Internisten Vereniging

Uitgangsvraag

Hoe dienen we om te gaan met antitrombotica rondom een endoscopische ingreep?

Introduction

The Dutch Society of Gastroenterology and Hepatology and the Society of Internal Medicine previously published separated guidelines on endoscopy in patients on antiplatelets or anticoagulant therapy in 2016. This is a joint update of the previous guidelines and a supplement of the recently updated Dutch National guideline on Antithrombotic Therapy and Interventions.

For all patients on antiplatelets or anticoagulants we state that there is an increased risk of post-procedure bleeding compared to patients not on these drugs. Therefore, the management of antithrombotic drugs is a balance of risks of bleeding from the procedure versus the risk of thrombosis. Bleeding secondary to high-risk endoscopic procedures can often be controlled by further endoscopic therapeutic measures and is rarely fatal. A thrombotic stroke may result in lifelong disability, and a major cardiac event may result in death. Not only do the risks of thrombosis vs bleeding need to be assessed on an individual patient basis, but patients should be fully informed, and involved in this decision-making process. The risk of a potentially catastrophic thrombotic event such as a stroke may not be acceptable to a patient even if that risk is very low.

Search and select

To answer the clinical question, the ESGE and BSG guideline was used: Endoscopy in patients on antiplatelet or anticoagulant therapy: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guideline update (Veitch, 2021), which is an update of the previous version (Veitch, 2016). Development of this guideline comply with the requirements of the National Institute for Health and Care Excellence (NICE). The literature review was adopted. No additional systematic review of the literature was performed.

Summary of literature

Aspirin

When given as long-term secondary prevention aspirin reduces vascular events by approximately one-third and vascular deaths by about one-sixth. In patients on long-term Low-dose aspirin for secondary prevention, aspirin interruption was associated with a threefold increased risk of cardiovascular or cerebrovascular events, and 70% of these events occurred within 7–10 days after interruption (Biondi-Zoccai, 2006 and Maulaz, 2005). In a randomised controlled trial (RCT) of 220 patients on low-dose aspirin for secondary prevention undergoing non-cardiac surgery, patients were randomised to continuation or temporary replacement of aspirin by placebo (Oscarsson, 2010). Major cardiac events occurred within 30 days in 1.8% of the aspirin group compared with 9% in the placebo group

(p=0.02). No difference in haemorrhagic complications was seen between the two groups. The risks related to continuation or discontinuation of aspirin for endoscopy are discussed in the sections on endoscopic procedures, and recommendations made accordingly. With regard to patients on a Direct Oral Anticoagulants (DOAC) and a single antiplatelet agent, such as aspirin, the AFIRE trial randomised patients with atrial fibrillation (AF) and stable coronary artery disease to rivaroxaban alone versus rivaroxaban and a single antiplatelet. They demonstrated that rivaroxaban alone was non-inferior for the primary efficacy endpoint (a composite of thromboembolic events or death from any cause) and superior for the primary safety endpoint of major bleeding. However, this trial was not sufficiently powered to address the risk of stent thrombosis (Yasuda, 2019). For patients with documented coronary artery disease and an indication for formal anticoagulation, for example, AF, then a life-long single antiplatelet such as aspirin is no longer recommended, beyond the antiplatelet duration required postcoronary stent insertion, in the latest ESC guidelines (Knuuti, 2020). However, late stent thrombosis (1–12 months poststent implantation) and very late stent thrombosis (beyond 12 months poststent implantation) occur with a reported incidence of 0.5%–1.0% and 0.2%–0.4%, respectively, and stent thrombosis is associated with a 4%–45% mortality (Gori, 2019). Furthermore, technical aspects of the procedure, for example, left main stents, may have an essential bearing on the subsequent risk of stent thrombosis. The trials addressing whether a long-term antiplatelet agent is needed in patients that have stents and require a DOAC, which suggest a DOAC alone may be safe, are not sufficiently powered to look at the important endpoint of stent thrombosis (Yasuda, 2019 and Lopes, 2019). Many consultant interventional cardiologists in the UK recommend their patients remain on a single antiplatelet agent if they have stents and need a long term DOAC, although this will very much vary on an individual case-by- case basis. Therefore, in patients with coronary stents who are taking a DOAC the cessation of the single antiplatelet agent should always be discussed in advance with the consultant interventional cardiologist responsible for the patient's care. Following the publication of three RCTs in 2018 the use of aspirin in primary prevention in cardiovascular disease is no longer routinely recommended and should only be considered, on a case-by-case basis, in those with a very high individual risk of cardiovascular events (Dasa, 2021).

P2Y12-receptor antagonists

Antiplatelet drugs have a rapid onset of action, and irreversibly inhibit platelet activity. Clopidogrel, prasugrel and ticagrelor are antagonists of the P2Y12 receptor on platelets. Clopidogrel plus aspirin is more potent than aspirin alone (Budaj, 2002). For clopidogrel, platelet function returns to normal 5–7 days after withdrawal of the drug (Korte, 2011). Prasugrel and ticagrelor are more rapidly acting and more potent platelet receptor antagonists than clopidogrel. Clopidogrel monotherapy may be used following a thromboembolic cerebrovascular accident, or for peripheral vascular disease. P2Y12 receptor antagonists are frequently used as DAPT with aspirin in acute coronary syndrome (ACS) and after placement of coronary stents. Patients on DAPT, with aspirin and a P2Y12 receptor antagonist, particularly in the context of coronary artery stents, are at high risk of thrombosis if drug therapy is discontinued. Without antiplatelet therapy coronary stents are at high risk of occlusion due to thrombosis, and this confers an approximate 40% risk of acute myocardial infarction or death. In one study, discontinuation of DAPT was associated with an HR of 161 for these events (Iakovou, 2005). DAPT is generally prescribed for 12 months after drug eluting stents (DES) implantation, though there have been occasional reported instances of thrombosis after this duration. Prasugrel and ticagrelor are now the main drugs of choice used for ACS in the UK. Prasugrel has been shown in a large UK observational series to be associated with a lower mortality (Olier, 2018). This has been

confirmed in a large randomised open-label trial (Schüpke, 2019). The latest NICE guidelines for ACS now recommend prasugrel is used as the first line agent in ACS, unless the patient is on anticoagulant therapy, in which case clopidogrel is recommended. Clopidogrel is generally the first choice of P2Y12 inhibitor in patients undergoing elective percutaneous coronary intervention (PCI) and the current guidelines recommend a 6 month course of DAPT post elective PCI (Knuuti, 2020). Where temporary cessation of P2Y12 inhibitors in patients with stents has been agreed, after discussion with the responsible consultant interventional cardiologist, then stopping the P2Y12 inhibitors 7 days pre procedure will minimize the bleeding risk. However, it should be noted that, depending on the P2Y12 agent, this time can be shortened dependent on the P2Y12 agent in use. In patients with a very high risk of stent thrombosis there may also be a role for bridging either with intravenous cangrelor and/or GIIbIIIa agents. However, the role of such bridging agents is beyond the remit of this guideline and this decision should be made along with the responsible consultant interventional cardiologist on a case-by-case basis (Valgimigli, 2018). Bare metal stents (BMS), which only require 1 month of DAPT, are now much less frequently used and the national BCIS audit shows they are used in less than 15% of cases in the UK, and many units no longer even stock them. Their main indication is for use in patients with a high bleeding risk or requiring urgent major surgery. Many UK units now use BioFreedom DES, these are polymer-free drug coated stents, which have a license of 1 month of DAPT and are superior to BMS with respect to major safety endpoints including bleeding and restenosis rates (Urban, 2015). Finally, there is increasing evidence that with a number of third generation DESs 1 month of DAPT can safely be used in patients at high bleeding risk without an increase in ischaemic events (Kandzari, 2020; Varenne, 2017 and Watanabe, 2019). A single antiplatelet agent is continued in all cases after discontinuation of DAPT, this tends to be aspirin. In some cases, for example, patients who had a previous stroke, the patients may have aspirin stopped at the end of the DAPT course and clopidogrel continued long-term. The important issue of a single antiplatelet agent in patients on long-term DOACs is discussed in the previous section.

Finally, in patients on a DOAC for AF and stroke prophylaxis who need DAPT after stent implantation, evidence from trials such as the RE-DUAL trial indicate that much shorter courses of triple therapy followed by a course of DOAC and clopidogrel alone are safer than previous practice of triple therapy up to a year (Cannon, 2017). The European Society of Cardiology and NICE guidelines, for both ACS and elective stenting, now support shorter durations of triple therapy followed by a DOAC and clopidogrel as the current standard of care (Knuuti, 2020; Collet, 2021 and Ibanez, 2018).

The duration of DAPT post-PCI may also depend on a number of other factors, beyond the scope of this guideline. Therefore, in patients with coronary stents, we recommend that the endoscopist discusses the plan, with respect to potential DAPT cessation, with a consultant interventional cardiologist. Ideally this should be the consultant interventional cardiologist responsible for the patient's care, who did the stent procedure.

Warfarin and heparin

Updated literature searches were conducted on the use of warfarin and heparin in patients undergoing endoscopy. There were no new data to indicate a change to the existing protocols, as described in the previous guideline (Veitch, 2016).

DOACs

DOACs have been a major advance in anticoagulant therapy. Dabigatran is an inhibitor of thrombin, and rivaroxaban, apixaban and edoxaban inhibit FXa. They do not need routine monitoring, and INR and activated partial thromboplastin time (aPTT) are unreliable indicators of anticoagulant activity. Unlike warfarin they have a rapid onset of action and full

anticoagulant activity is established within 3 hours of the first dose. They have relatively short half-lives, but these may be prolonged in renal failure, particularly for dabigatran. In patients undergoing a high-risk procedure with a low thrombotic risk we recommend that the last dose of rivaroxaban, apixaban or edoxaban is taken 3 days before the procedure. Dabigatran may have to be stopped for longer than this, however, when renal function is significantly reduced (Schulman, 2015).

For patients on dabigatran with CrCl of 30–50 mL/min we recommend that the last dose of the drug is 5 days before the procedure. Dabigatran therapy is contraindicated in patients with CrCl<30 mL/min. eGFR is a suitable alternative measurement of renal function, and the same numerical values apply for the purposes of these guidelines. If a patient on any DOAC is clinically deteriorating, his/her renal function should be checked before the procedure.

These recommendations are supported by the findings of the PAUSE trial (Douketis, 2019). Three thousand and seven patients on apixaban, dabigatran or rivaroxaban due for elective interventional procedures had a standardised interruption of therapy: last dose of drug 2 days before low-risk procedures (including diagnostic GI endoscopy) and 3 days before high-risk procedures (including high-risk therapeutic GI endoscopy; eg, polypectomy). This was extended to last dose 5 days before a high-risk procedure for dabigatran patients with CrCL<50 mL/min. Resumption of therapy occurred at 1 day after low bleeding risk procedures and 2–3 days after high bleeding risk procedures. Low rates of major bleeding or arterial thromboembolism were observed. Low rates of venous thromboembolism were also observed although this was not a primary study outcome. We have maintained the recommendation to omit the morning dose of DOAC prior to low-risk endoscopic procedures, although the PAUSE trial demonstrates the safety of omitting the DOAC for 1 day before a low-risk endoscopic procedure if desired.

Bridging of anticoagulant therapy

Unfractionated heparin (UFH) and LMWH (LMWH) have short half-lives compared with warfarin and can be employed as an anticoagulation ‘bridge’ while warfarin is temporarily discontinued for endoscopic procedures considered to have a significant risk of bleeding. UFH is administered by continuous intravenous infusion and LMWH by subcutaneous injection once or two times a day. The former requires an inpatient stay in hospital while warfarin is discontinued, and then re-introduced, and also requires frequent monitoring of aPTT; the latter can often be managed in an outpatient setting without monitoring of anticoagulation levels. Some cardiologists have a preference for UFH for bridging warfarin in patients with metal heart valves. A meta-analysis demonstrated higher rates of bleeding in patients with mechanical heart valves bridged with LMWH versus UFH, but numbers were small in the LMWH studies (Passaglia, 2015). A small multicentre registry study found no difference in adverse events between patients bridged with UFH or LMWH in this context (Spyropoulos, 2008), and bridging with LMWH is now commonplace. Guidelines from the American Heart Association and American College of Cardiology do not recommend one strategy over the other (Otto, 2021). Prosthetic metal heart valves in the mitral position are at particularly high risk of thrombosis if warfarin is temporarily discontinued for 5–7 days. Heparin bridging for patients with a bi-leaflet mechanical aortic valve replacement in the absence of AF is considered unnecessary in guidelines from the British Society of Haematology (Keeling, 2016) and from the American College of Cardiology/American Heart Association (Nishimura, 2017),but it is recommended in guidelines from the ESC and the European Association for Cardio-Thoracic Surgery (Baumgartner, 2017). There are no high quality studies to inform us, and consequently levels of evidence are low quality in all three guidelines. We have now placed mechanical aortic valve replacement in the high-risk category requiring bridging, in line with European guidelines, but this should be decided in conjunction with local cardiology or cardiothoracic surgery services given the uncertainty.

This should always be discussed with the consultant cardiologist responsible for the patient's care. The risk of thromboembolism with AF increases with additional cardiovascular factors such as hypertension, heart failure and diabetes and this risk has been quantified by the CHADS2 score (annual risk of stroke increasing from 1.9% with a score of 1 to 18.2% with a score of 6). This has been updated with the CHA2DS2VASc scoring system in which the annual risk of stroke increases from 1.3% with a score of 1 to 15.2% with score of 9. A randomised, prospective, double-blind placebo-controlled trial was conducted in 1884 patients with AF undergoing a variety of operative procedures including approximately 50% GI endoscopy (Douketis, 2015). Patients were randomised to LMWH or placebo, and risk factors were well matched. Thirty-eight percent of the patients had CHADS2 scores>3, <2% had mitral stenosis and ≤3.4% had CHADS2 scores of 5 or 6. There was no significant difference in rates of thromboembolism between the LMWH and placebo groups, but there was a significant increase in major haemorrhagic events in the LMWH group versus placebo (3.2% vs 1.3%). Caution should be exercised when interpreting the results in the high-risk thromboembolic groups as the study was not designed or statistically powered to examine these categories. The previous BSG/ESGE guidelines (Veitch, 2016) do not recommend bridging for non-valvular AF, ASGE guidelines (Acosta, 2015) recommend bridging with LMWH for CHA2DS2VASc>2 and the APAGE/APSDE guidelines (Chan, 2018) recommend this for CHA2DS2VASc>5. CHADS2 scores are unfortunately not directly equivalent to CHA2DS2VASc scores. Further research on the benefits of heparin bridging is required in high-risk patients with non-valvular AF on warfarin in order to determine the optimum approach, but it would be reasonable to consider bridging patients with CHADS2 scores >5 as recommended by the British Society of Haematology (Keeling, 2016). This applies to patients with AF and a previous stroke or transient ischaemic attack (TIA), and three of the following factors: congestive cardiac failure, hypertension (>140/90 mm Hg or on antihypertensive medication), age>75 years or diabetes mellitus. Heparin bridging is also recommended for patients with AF who have had a stroke or TIA within 3 months (Keeling, 2016). Bridging with LMWH has also been studied in patients on DOACs. In a German registry, heparin bridging versus no bridging led to a higher rate of major bleeding (2.7% vs 0.5%, p=0.01) with no reduction in thromboembolism (Beyer-Westendorf, 2014). In the RELY trial bridging of dabigatran with LMWH resulted in higher major bleeding rates compared with no bridging (6.5% vs 1.8%, p<0.001) with no difference in thrombosis rates between the groups (Douketis, 2015). In a Japanese study of 16 977 patients on warfarin or DOACs undergoing a variety of high-risk endoscopy procedures a propensity matched analysis demonstrated a significant increase in postprocedure GI bleeding and thromboembolism in patients who were bridged with heparin (Nagata, 2018). It should be noted that all patients were bridged with UFH rather than LMWH. For colonoscopy in patients on warfarin who were bridged with LMWH, several studies have demonstrated an increase in postpolypectomy bleeding without a decrease in thromboembolic events (Ishigami, 2017; Lin, 2018 and Ono, 2019). Bridging with LMWH should, of course still be advocated for those patients on warfarin at high risk of thromboembolism, but patients should be advised of the increased risk of post-procedure bleeding. The safety of temporary cessation of DOAC therapy, without bridging, is supported by the findings of the PAUSE trial (Douketis, 2019). Patients with a history of venous thromboembolism within 3 months of commencing anticoagulant therapy are at high risk of recurrent thrombosis if anticoagulation is interrupted. Most of these patients are now commenced on a DOAC rather than warfarin, and bridging would not be recommended. Ideally we should not interrupt anticoagulation in this high-risk group due to the risk of thrombosis; an elective low-risk procedure could be performed without interrupting anticoagulation if necessary, but it may be preferable to defer a high-risk procedure beyond 3 months anticoagulation if safe to do so. Patients with thrombophilia syndromes should be discussed with a haematologist. Factor V Leiden and the

common prothrombin mutation F2G20210A are low-risk thrombophilias and bridging is not required. Patients with deficiencies of antithrombin, protein C or protein S are at higher risk of thrombosis, but in most of these patients bridging therapy will not be required.

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Voor deze module over het antitrombotisch beleid bij endoscopische ingrepen is de ESGE/BSG-richtlijn (Veitch, 2021) als uitgangspunt gebruikt. De door hen bepaalde bewijskracht varieerde van redelijk tot zeer laag. Voor het grootste deel van de door hen geformuleerde aanbevelingen geldt dat deze gebaseerd zijn op een lage tot zeer lage bewijskracht. Er is dan ook sprake van een kennisvraag.

Voor het opstellen van de aanbevelingen is de werkgroep nagegaan in hoeverre de aanbevelingen passend zijn bij de Nederlandse praktijk. Hierbij is bijvoorbeeld rekening gehouden met het gegeven dat de zorg rondom o.a. de monitoring van de VKA belegd is bij de Trombosedienst. Daarnaast heeft de werkgroep gekeken naar eventuele discrepanties met de aanbevelingen uit de modules over periprocedureel beleid en de daarbij aansluitende doorvertaling in de Landelijke Transmurale Afspraak (LTA) Antistollingszorg. Tot slot is rekening gehouden met overige overwegingen, die in de tekst hieronder zijn geformuleerd.

Voor aanvang van een endoscopische ingreep bij patiënten met antitrombotische therapie moet degene die de ingreep doet het volgende overwegen: de noodzaak van de procedure en het risico op: 1. bloedingen gerelateerd aan de endoscopische interventie in samenhang met de antitrombotische middelen en 2. trombo-embolische gebeurtenissen bij het onderbreken van de antitrombotische therapie. Zie hiervoor ook de module over periprocedureel beleid.

Daarnaast moeten alternatieven voor diagnostiek (zoals videocapsule of radiologie) worden overwogen als ook het gebruik van overbruggende medicatie in de vorm van subcutane of intraveneuze antitrombotische therapie en laboratoriumtesten om antitrombotische therapie te monitoren. Het is belangrijk om in ogenschouw te nemen dat potentiële trombo-embolische gebeurtenissen die plaatsvinden na het onderbreken van de therapie (zoals een herseninfarct of coronaire stenttrombose) ernstige consequenties hebben terwijl bloedingen na hoog-risico procedures, hoewel vaker voorkomend, zelden leiden tot hoge morbiditeit of mortaliteit. Overleg met de patiënt en eventueel zijn antitrombotische therapie voorschrijvende arts voorafgaand aan de procedure is dan ook noodzakelijk om te beoordelen of de medicatie kan worden onderbroken of worden overbrugd.

Electieve therapeutische endoscopie wordt zo mogelijk uitgesteld tot na het afronden van een tijdelijke behandeling met antitrombotische therapie (zoals bij diep veneuze trombose (DVT)) of tijdelijke behandeling met dubbele trombocytenaggregatieremming (zoals bij coronaire stents)). Als de beslissing is genomen een endoscopie te verrichten bij een patiënt onder antitrombotische therapie, is de noodzaak deze te onderbreken of couperen afhankelijk van de situatie. Het risico op een trombo-embolische complicatie na het couperen/onderbreken van anticoagulantia, is sterk afhankelijk van de indicatie en het uitgangsrisico van de patiënt. Mede op basis hiervan zijn verschillende indelingen bekend, op grond waarvan geadviseerd wordt al dan niet te bridgen, d.w.z. ‘overbruggende therapie’ te geven met therapeutische doseringen van (korter werkende) anticoagulantia zoals bijv. LMWH. Een belangrijke indicator van het risico op trombo-embolie bij atriumfibrilleren is de CHA2DS2-VASc-score. Het onderbreken van VKA dient in overleg te gaan met de

trombosedienst, voor adviezen omtrent het onderbreken van VKA wordt verwezen naar de module Periprocedureel beleid bij VKA.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Zoals eerder gesteld geldt voor alle patiënten die antitrombotische medicatie gebruiken dat er een verhoogd risico is op post-endoscopische bloedingen ten opzichte van patiënten die niet dergelijke medicatie gebruiken. Het is dan ook belangrijk om met patiënten (en/of hun verzorgers) zowel de risico's van het onderbreken als het risico op een bloeding bij het continueren van deze medicatie te bespreken. Het is hierbij belangrijk om alternatieven te overwegen zoals het beperken tot alleen diagnostisch onderzoek (incl. biopteren) of het verrichten van non-invasieve beeldvorming (zoals bijv. CT-colonografie). Hetzelfde geldt voor de timing van het onderzoek, zoals het uitstellen van de procedure totdat eventuele dubbele plaatjes aggregatie veilig kan worden onderbroken. Het is belangrijk om dit met de patient te bespreken zodat er in gezamenlijkheid een besluit genomen kan worden. Voor de patient is het belangrijk dat duidelijk is wanneer de antitrombotische medicatie gestopt en vervolgens hervat kan worden en wie het aanspreekpunt hiervoor is. Verder verwijzen we hiervoor naar de module communicatie met patiënten bij antitrombotisch beleid.

Kosten (middelenbeslag)

Het onderbreken van antitrombotische therapie gaat niet gepaard met extra kosten. Wel zal een bezoek aan de spoedeisende hulp vanwege een post-procedurele bloeding vanwege het niet onderbreken van de medicatie tot extra kosten leiden, hetzelfde geldt voor bijvoorbeeld een CVA na het tijdelijk staken van de antitrombotische medicatie.

Aanvaardbaarheid, haalbaarheid en implementatie

Het aantal jaarlijks uitgevoerde endoscopische procedures in Nederland is de afgelopen jaren fors toegenomen. Een aanzienlijk deel van deze endoscopische procedures betreffen therapeutische procedures waarbij de kans op complicaties zoals een bloeding verhoogd is, zeker wanneer de patiënt ook antitrombotische therapie gebruikt. Om het risico op bloedingen te reduceren zal het veelal nodig zijn deze medicatie bij therapeutische ingrepen (bijv. poliepectomie) tijdelijk te onderbreken. Dit kan echter ook leiden tot een verhoogd risico op trombo-embolische complicaties zoals een CVA of een geoccludeerde coronairstent. Deze module is een aanvulling op de modules over Periprocedureel beleid en heeft als doel te voorkomen dat medicatie onnodig wordt onderbroken, bijvoorbeeld voorafgaand aan een diagnostische endoscopie, waardoor de patiënt minder risico heeft op een trombo-embolische gebeurtenis. Deze module over het beleid antitrombotische therapie rondom endoscopische procedures richt zich naast MDL-artsen ook op andere disciplines die endoscopieën van de tractus digestivus verrichten zoals internisten, chirurgen en MDL-verpleegkundigen. Bezwaren ten aanzien van de adviezen en aanbevelingen die worden gegeven in, dan wel belemmerende factoren voor de implementatie zijn niet te verwachten.

Aanbevelingen

1. Algemene aanbevelingen

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Voorafgaand aan het uitvoeren van een endoscopische procedure bij patiënten die antitrombotische therapie gebruiken, moet een afweging gemaakt worden tussen enerzijds het bloedingsrisico van de endoscopische procedure, waarbij ook de vorm van antistolling een rol speelt en anderzijds het risico op trombo-embolische gebeurtenissen bij het onderbreken van de antitrombotische therapie. Het is daarom van belang om deze risico's

voorafgaand aan de procedure in kaart te brengen en waar nodig te overleggen met de voorschrijver van de antitrombotica.

Algemene aanbevelingen

Bespreek met de patiënt het trombotisch risico als gevolg van het staken van de antitrombotica alsook het bloedingsrisico bij het continueren van de antitrombotica.

Bepaal het bloedingsrisico van de endoscopische procedure. Maak hierbij gebruik van Tabel 1.

Bepaal het trombo-embolisch risico, indien er sprake is van een hoog bloedingsrisico. Maak hierbij gebruik van Tabel 2.

Overleg bij patiënten met een hoog bloedingsrisico én een hoog trombo-embolisch risico met de voorschrijver van de antitrombotica om tot een gewogen besluit te komen.

2. Aanbeveling P2Y12-receptor antagonisten

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Voorafgaand aan het uitvoeren van een endoscopische procedure bij patiënten die P2Y12-receptor antagonisten gebruiken, moet een afweging gemaakt worden tussen enerzijds het bloedingsrisico van de endoscopische procedure, en anderzijds het risico op trombo-embolische gebeurtenissen bij het onderbreken van de antitrombotische therapie. Bij ingrepen waarbij er sprake is van een laag bloedingsrisico kunnen de P2Y12-receptor antagonisten worden gecontinueerd. Bij ingrepen met een hoog bloedingsrisico dient er rekening gehouden te worden met het trombotisch risico waarbij o.a. de indicatie voor de antistolling en de duur van de onderbreking meegewogen worden. In sommige gevallen kan overleg met de voorschrijvend arts noodzakelijk zijn.

Patiënten met monotherapie trombocytenaggregatieremmers (TAR)

Laag bloedingsrisico
Continueer salicylzuur/carbasalaatcalcium (ASA) en/of clopidogrel/ticagrelor/prasugrel (P2Y12 receptor antagonist) bij patiënten die een endoscopische procedure met een laag bloedingsrisico ondergaan.

Hoog bloedingsrisico en laag trombotisch risico
Continueer acetylsalicylzuur/carbasalaatcalcium (ASA) bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan en waarbij sprake is van een laag trombotisch risico.
Onderbreek de P2Y12-receptor antagonist (prasugrel 7 dagen, clopidogrel 5 dagen en ticagrelor 3 dagen) voorafgaand aan de endoscopie bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan en waarbij er sprake is van een laag trombotisch risico. Herstart P2Y12 receptor antagonist na 48 tot 72 uur.

Hoog bloedingsrisico en hoog trombotisch risico
Continueer de ASA of de P2Y12-receptor antagonist bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan en waarbij sprake is van een hoog trombotisch risico.

Patiënten met duale therapie trombocytenaggregatieremmers (TAR)
Overleg voorafgaand aan de endoscopische procedure altijd met de voorschrijvend arts over het beleid van eventueel tijdelijk staken van de een van de TARs van de duale therapie.

Laag bloedingsrisico
Continueer salicylzuur/carbasalaatcalcium (ASA) en clopidogrel/ticagrelor/prasugrel (P2Y12 receptor antagonist) bij patiënten die een endoscopische procedure met een laag bloedingsrisico ondergaan.

Hoog bloedingsrisico en laag trombotisch risico
Onderbreek de P2Y12 receptor antagonist (prasugrel 7 dagen preoperatief, clopidogrel 5 dagen preoperatief en ticagrelor 3 dagen preoperatief) bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan en waarbij sprake is van een laag trombotisch risico. Continueer de ASA. Herstart P2Y12 receptor antagonisten binnen 48 uur na de endoscopische procedure.

Hoog bloedingsrisico en hoog trombotisch risico
Overweeg, in overleg met de voorschrijvend arts om een van de TAR's tijdelijk te onderbreken bij patiënten die 3-6 maanden duale therapie hebben ontvangen en waarbij er geen ischemisch event is opgetreden. Herstart duale therapie binnen 48 uur na de endoscopische procedure.

Herstarten algemeen
Herstart ASA/clopidogrel/ticagrelor/prasugrel of een andere plaatjesremmer na de endoscopische procedure met de dosis, die past bij het voorgeschreven middel.

Volg hierbij de stappen uit het stroomschema 'Beleid bij monotherapie of duale therapie TAR'.

3. Aanbeveling vitamine K-antagonisten (VKA)

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
Voorafgaand aan het uitvoeren van een endoscopische procedure bij patiënten die VKA gebruiken, moet een afweging gemaakt worden tussen enerzijds het bloedingsrisico van de endoscopische procedure, en anderzijds het risico op trombo-embolische gebeurtenissen bij het onderbreken van de VKA. Bij ingrepen waarbij er sprake is van een laag bloedingsrisico kunnen de VKA worden gecontinueerd. Bij ingrepen met een hoog bloedingsrisico dient er rekening gehouden te worden met het trombotisch risico, waarbij o.a. de indicatie voor de antistolling, het type VKA en de duur van de onderbreking meegewogen worden. Afstemming met de Trombosedienst is hierbij belangrijk. De beslissing om rondom een operatie/ingreep te overbruggen met antistollingsbehandeling hangt af van het periprocedurele trombotisch risico.

Vitamine K-antagonisten (VKA)

Laag bloedingsrisico
Continueer VKA bij patiënten die een endoscopische procedure met een laag bloedingsrisico ondergaan.

Hoog bloedingsrisico en laag trombotisch risico

Stop VKA bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan en waarbij sprake is van een laag trombotisch risico en stem het beleid met betrekking tot het staken af met de Trombosedienst en benoem hierbij:

- Dat de streef-INR ≤ 1,5 is;
- Dat de VKA herstart kan worden 48 uur na de endoscopische procedure, met 1.5-2 maal de gebruikelijke dagelijkse dosis.

Hoog bloedingsrisico en hoog trombotisch risico

Stop VKA bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan en waarbij sprake is van een hoog trombotisch risico. Stem het beleid met betrekking tot staken en de overbruggingstherapie af met de Trombosedienst. Benoem hierbij:

- Dat de INR 48 uur voorafgaand aan de endoscopische procedure gecheckt moet worden;
    - Start met een therapeutische dosis LMWH, indien INR <2.0. Geef 24 uur (1dd) of 12 uur (2dd) voorafgaand aan de endoscopische ingreep de laatste dosis.
    - Indien er gebruik wordt gemaakt van ongefractioneerde heparine, staak de toediening via het infuus vier uur voorafgaand aan de endoscopische procedure.
- Dat de INR op de dag van de endoscopische procedure gecheckt moet worden, waarbij de streef-INR ≤1,5 is;
- Dat de VKA herstart kan worden op de dag na de endoscopische procedure.

Herstarten LMWH

- Geef een profylactische dosis LMWH, zolang er geen therapeutische LMWH wordt herstart.
- Herstart de therapeutische LMWH tenminste 48 uur na de endoscopische procedure.
- De LMWH kan worden gestaakt indien de INR eenmaal boven 2.0 (indien de streefwaarde 2,0 tot 3,0 is) of 2,5 (indien de streefwaarde 2,5 tot 3,5 is).

Volg hierbij de stappen uit het stroomschema ‘Beleid bij behandeling met VKA’.

4. Aanbeveling DOAC

Rationale van de aanbeveling: weging van de argumenten voor en tegen de interventie

Voorafgaand aan het uitvoeren van een endoscopische procedure bij patiënten die DOAC’s gebruiken, moet een afweging gemaakt worden tussen enerzijds het bloedingsrisico van de endoscopische procedure, en anderzijds het risico op trombo-embolische gebeurtenissen bij het onderbreken van de DOAC’s. Bij ingrepen waarbij er sprake is van een laag bloedingsrisico kunnen de DOAC’s worden gecontinueerd. Bij ingrepen met een hoog bloedingsrisico dient er rekening gehouden te worden met het trombotisch risico, waarbij o.a. de indicatie voor de antistolling, het type DOAC, de nierfunctie en de duur van de onderbreking meegewogen worden.

Directe Orale Anticoagulantia (DOAC)

Laag bloedingsrisico

Continueer DOAC bij patiënten die een endoscopische procedure met een laag bloedingsrisico ondergaan.

Hoog bloedingsrisico

Onderbreek de DOACs bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan, afhankelijk van het type DOAC en de nierfunctie:

- Xa-remmers: 48 uur voorafgaand aan de procedure;
- Dabigatran en eGFR >80 ml/min: 48 uur voorafgaand aan de procedure;
- Dabigatran en eGFR 50-80 ml/min: 72 uur voorafgaand aan de ingreep;
- Dabigatran en eGFR 30-50 ml/min: 96 uur voorafgaand aan de procedure.

Herstart de DOACs 48 uur na de endoscopische procedure bij een hoog trombotisch risico en 72 uur na de endoscopische procedure bij een laag trombotisch risico.

Volg hierbij de stappen uit het stroomschema 'Beleid bij behandeling met DOAC'.

Kennisvragen

Wat is de juiste timing van het herstarten van antitrombotische therapie bij patiënten die een endoscopische procedure ondergaan?

Literatuur

ASGE Standards of Practice Committee; Acosta RD, Abraham NS, Chandrasekhara V, Chathadi KV, Early DS, Eloubeidi MA, Evans JA, Faulx AL, Fisher DA, Fonkalsrud L, Hwang JH, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Shaukat A, Shergill AK, Wang A, Cash BD, DeWitt JM. The management of antithrombotic agents for patients undergoing GI endoscopy. Gastrointest Endosc. 2016 Jan;83(1):3-16. doi: 10.1016/j.gie.2015.09.035. Epub 2015 Nov 24. Erratum in: Gastrointest Endosc. 2016 Mar;83(3):678. PMID: 26621548.

Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun;133(6 Suppl):160S-198S. doi: 10.1378/chest.08-0670. PMID: 18574265.

Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017 Sep 21;38(36):2739-2791. doi: 10.1093/eurheartj/ehx391. PMID: 28886619.

Beyer-Westendorf J, Gelbricht V, Förster K, Ebertz F, Köhler C, Werth S, Kuhlisch E, Stange T, Thieme C, Daschkow K, Weiss N. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J. 2014 Jul 21;35(28):1888-96. doi: 10.1093/eurheartj/eht557. Epub 2014 Jan 6. PMID: 24394381.

Biondi-Zoccai GG, Lotrionte M, Agostoni P, Abbate A, Fusaro M, Burzotta F, Testa L, Sheiban I, Sangiorgi G. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. Eur Heart J. 2006 Nov;27(22):2667-74. doi: 10.1093/eurheartj/ehl334. Epub 2006 Oct 19. PMID: 17053008.

Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, Nordaby M, Kleine E, Harper R, Manassie J, Januzzi JL, Ten Berg JM, Steg PG, Hohnloser SH; RE-DUAL PCI Steering Committee and Investigators. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med. 2017 Oct 19;377(16):1513-1524. doi: 10.1056/NEJMoa1708454. Epub 2017 Aug 27. PMID: 28844193.

Chan FKL, Goh KL, Reddy N, Fujimoto K, Ho KY, Hokimoto S, Jeong YH, Kitazono T, Lee HS, Mahachai V, Tsoi KKF, Wu MS, Yan BP, Sugano K. Management of patients on antithrombotic agents undergoing emergency and elective endoscopy: joint Asian Pacific Association of Gastroenterology (APAGE) and Asian Pacific Society for Digestive Endoscopy (APSDE) practice guidelines. Gut. 2018 Mar;67(3):405-417. doi: 10.1136/gutjnl-2017-315131. Epub 2018 Jan 13. PMID: 29331946; PMCID: PMC5868286.

Choudari CP, Rajgopal C, Palmer KR. Acute gastrointestinal haemorrhage in anticoagulated patients: diagnoses and response to endoscopic treatment. Gut. 1994 Apr;35(4):464-6. doi: 10.1136/gut.35.4.464. PMID: 8174982; PMCID: PMC1374792.

Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021 Apr 7;42(14):1289-1367. doi: 10.1093/eurheartj/ehaa575. Erratum in: Eur Heart J. 2021 May 14;42(19):1908. Erratum in: Eur Heart J. 2021 May 14;42(19):1925. Erratum in: Eur Heart J. 2021 May 13;: PMID: 32860058.

Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, Yue P, Bronson MD, Lu G, Conley PB, Verhamme P, Schmidt J, Middeldorp S, Cohen AT, Beyer-Westendorf J, Albaladejo P, Lopez-Sendon J, Demchuk AM, Pallin DJ, Concha M, Goodman S, Leeds J, Souza S, Siegal DM, Zotova E, Meeks B, Ahmad S, Nakamya J, Milling TJ Jr; ANNEXA-4 Investigators. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2019 Apr 4;380(14):1326-1335. doi: 10.1056/NEJMoa1814051. Epub 2019 Feb 7. PMID: 30730782; PMCID: PMC6699827.

Cuker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, Wirth D, Kaatz S. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. Am J Hematol. 2019 Jun;94(6):697-709. doi: 10.1002/ajh.25475. Epub 2019 Apr 16. PMID: 30916798.

Dasa O, Pepine CJ, Pearson TA. Aspirin in Primary Prevention: What Changed? A Critical Appraisal of Current Evidence. Am J Cardiol. 2021 Feb 15;141:38-48. doi: 10.1016/j.amjcard.2020.11.014. Epub 2020 Nov 19. PMID: 33221264.

14 Budaj A, Yusuf S, Mehta SR, Fox KA, Tognoni G, Zhao F, Chrolavicius S, Hunt D, Keltai M, Franzosi MG; Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. Circulation. 2002 Sep 24;106(13):1622-6. doi: 10.1161/01.cir.0000029926.71825.e2. PMID: 12270853.

Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, Garcia DA, Jacobson A, Jaffer AK, Kong DF, Schulman S, Turpie AG, Hasselblad V, Ortel TL; BRIDGE Investigators. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med. 2015 Aug 27;373(9):823-33. doi: 10.1056/NEJMoa1501035. Epub 2015 Jun 22. PMID: 26095867; PMCID: PMC4931686.

Douketis JD, Healey JS, Brueckmann M, Eikelboom JW, Ezekowitz MD, Fraessdorf M, Noack H, Oldgren J, Reilly P, Spyropoulos AC, Wallentin L, Connolly SJ. Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients who had an elective surgery or procedure. Substudy of the RE-LY trial. Thromb Haemost. 2015 Mar;113(3):625-32. doi: 10.1160/TH14-04-0305. Epub 2014 Dec 4. PMID: 25472710.

Douketis JD, Spyropoulos AC, Duncan J, Carrier M, Le Gal G, Tafur AJ, Vanassche T, Verhamme P, Shivakumar S, Gross PL, Lee AYY, Yeo E, Solymoss S, Kassis J, Le Templier G, Kowalski S, Blostein M, Shah V, MacKay E, Wu C, Clark NP, Bates SM, Spencer FA, Arnaoutoglou E, Coppens M, Arnold DM, Caprini JA, Li N, Moffat KA, Syed S, Schulman S. Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral

Anticoagulant. JAMA Intern Med. 2019 Nov 1;179(11):1469-1478. doi: 10.1001/jamainternmed.2019.2431. PMID: 31380891; PMCID: PMC6686768.

Eisenberg MJ, Richard PR, Libersan D, Filion KB. Safety of short-term discontinuation of antiplatelet therapy in patients with drug-eluting stents. Circulation. 2009 Mar 31;119(12):1634-42. doi: 10.1161/CIRCULATIONAHA.108.813667. Epub 2009 Mar 16. PMID: 19289638.

Gori T, Polimeni A, Indolfi C, Räber L, Adriaenssens T, Münzel T. Predictors of stent thrombosis and their implications for clinical practice. Nat Rev Cardiol. 2019 Apr;16(4):243-256. doi: 10.1038/s41569-018-0118-5. PMID: 30518952.

Hearnshaw SA, Logan RF, Lowe D, Travis SP, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. Gut. 2011 Oct;60(10):1327-35. doi: 10.1136/gut.2010.228437. Epub 2011 Apr 13. PMID: 21490373.

Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA. 2005 May 4;293(17):2126-30. doi: 10.1001/jama.293.17.2126. PMID: 15870416.

Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018 Jan 7;39(2):119-177. doi: 10.1093/eurheartj/ehx393. PMID: 28886621.

Ishigami H, Arai M, Matsumura T, Maruoka D, Minemura S, Okimoto K, Kasamatsu S, Saito K, Nakagawa T, Katsuno T, Yokosuka O. Heparin-bridging therapy is associated with a high risk of post-polypectomy bleeding regardless of polyp size. Dig Endosc. 2017 Jan;29(1):65-72. doi: 10.1111/den.12692. Epub 2016 Jul 28. PMID: 27368065.

Jamula E, Lloyd NS, Schwalm JD, Airaksinen KE, Douketis JD. Safety of uninterrupted anticoagulation in patients requiring elective coronary angiography with or without percutaneous coronary intervention: a systematic review and metaanalysis. Chest. 2010 Oct;138(4):840-7. doi: 10.1378/chest.09-2603. Epub 2010 Apr 30. PMID: 20435662.

January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014 Dec 2;130(23):e199-267. doi: 10.1161/CIR.0000000000000041. Epub 2014 Mar 28. Erratum in: Circulation. 2014 Dec 2;130(23):e272-4. PMID: 24682347; PMCID: PMC4676081.

Kandzari DE, Kirtane AJ, Windecker S, Latib A, Kedhi E, Mehran R, Price MJ, Abizaid A, Simon DI, Worthley SG, Zaman A, Choi JW, Caputo R, Kanitkar M, McLaurin B, Potluri S, Smith T, Spriggs D, Tolleson T, Nazif T, Parke M, Lee LC, Lung TH, Stone GW; Onyx ONE US/Japan Investigators. One-Month Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention With Zotarolimus-Eluting Stents in High-Bleeding-Risk Patients. Circ Cardiovasc Interv. 2020 Nov;13(11):e009565. doi: 10.1161/CIRCINTERVENTIONS.120.009565. Epub 2020 Nov 10. PMID: 33167705; PMCID: PMC7665241.

Keeling D, Tait RC, Watson H; British Committee of Standards for Haematology. Peri-operative management of anticoagulation and antiplatelet therapy. Br J Haematol. 2016 Nov;175(4):602-613. doi: 10.1111/bjh.14344. Epub 2016 Oct 7. PMID: 27714755.

Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020 Jan 14;41(3):407-477. doi: 10.1093/eurheartj/ehz425. Erratum in: Eur Heart J. 2020 Nov 21;41(44):4242. PMID: 31504439.

Korte W, Cattaneo M, Chassot PG, Eichinger S, von Heymann C, Hofmann N, Rickli H, Spannagl M, Ziegler B, Verheugt F, Huber K. Peri-operative management of antiplatelet therapy in patients with coronary artery disease: joint position paper by members of the working group on Perioperative Haemostasis of the Society on Thrombosis and Haemostasis Research (GTH), the working group on Perioperative Coagulation of the Austrian Society for Anesthesiology, Resuscitation and Intensive Care (ÖGARI) and the Working Group Thrombosis of the European Society for Cardiology (ESC). Thromb Haemost. 2011 May;105(5):743-9. doi: 10.1160/TH10-04-0217. Epub 2011 Mar 24. PMID: 21437351.

Li DF, Chang X, Fang X, Wang JY, Yu ZC, Wei C, Xiong F, Xu ZL, Zhang DG, Liu TT, Luo MH, Wang LS, Yao J. Colonoscopic post-polypectomy bleeding in patients on uninterruptedclopidogrel therapy: A systematic review and meta-analysis. Exp Ther Med. 2020 May;19(5):3211-3218. doi: 10.3892/etm.2020.8597. Epub 2020 Mar 12. PMID: 32266017; PMCID: PMC7132234.

Lin D, Soetikno RM, McQuaid K, Pham C, Doan G, Mou S, Shergill AK, Somsouk M, Rouse RV, Kaltenbach T. Risk factors for postpolypectomy bleeding in patients receiving anticoagulation or antiplatelet medications. Gastrointest Endosc. 2018 Apr;87(4):1106-1113. doi: 10.1016/j.gie.2017.11.024. Epub 2017 Dec 6. PMID: 29208464.

Little D, Chai-Adisaksopha C, Hillis C, Witt DM, Monreal M, Crowther MA, Siegal DM. Resumption of anticoagulant therapy after anticoagulant-related gastrointestinal bleeding: A systematic review and meta-analysis. Thromb Res. 2019 Mar;175:102-109. doi: 10.1016/j.thromres.2019.01.020. Epub 2019 Jan 30. PMID: 30743134.

Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, Averkov O, Bahit MC, Berwanger O, Budaj A, Hijazi Z, Parkhomenko A, Sinnaeve P, Storey RF, Thiele H, Vinereanu D, Granger CB, Alexander JH; AUGUSTUS Investigators. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. N Engl J Med. 2019 Apr 18;380(16):1509-1524. doi: 10.1056/NEJMoa1817083. Epub 2019 Mar 17. PMID: 30883055.

Majeed A, Ågren A, Holmström M, Bruzelius M, Chaireti R, Odeberg J, Hempel EL, Magnusson M, Frisk T, Schulman S. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood. 2017 Oct 12;130(15):1706-1712. doi: 10.1182/blood-2017-05-782060. Epub 2017 Aug 23. PMID: 28835439.

Marmo R, Koch M, Cipolletta L, Capurso L, Grossi E, Cestari R, Bianco MA, Pandolfo N, Dezi A, Casetti T, Lorenzini I, Germani U, Imperiali G, Stroppa I, Barberani F, Boschetto S, Gigliozzi A, Gatto G, Peri V, Buzzi A, Della Casa D, Di Cicco M, Proietti M, Aragona G, Giangregorio F, Allegretta L, Tronci S, Michetti P, Romagnoli P, Piubello W, Ferri B, Fornari F, Del Piano M, Pagliarulo M, Di Mitri R, Trallori G, Bagnoli S, Frosini G, Macchiarelli R, Sorrentini I, Pietrini L, De Stefano S, Ceglia T, Chiozzini G, Salvagnini M, Di Muzio D, Rotondano G; Italian registry on upper gastrointestinal bleeding (Progetto Nazionale Emorragie Digestive--PNED 2). Predicting mortality in non-variceal upper gastrointestinal bleeders: validation of the Italian PNED Score and Prospective Comparison with the Rockall

Score. Am J Gastroenterol. 2010 Jun;105(6):1284-91. doi: 10.1038/ajg.2009.687. Epub 2010 Jan 5. PMID: 20051943.

Maulaz AB, Bezerra DC, Michel P, Bogousslavsky J. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. Arch Neurol. 2005 Aug;62(8):1217-20. doi: 10.1001/archneur.62.8.1217. PMID: 16087761.

Nagata N, Sakurai T, Moriyasu S, Shimbo T, Okubo H, Watanabe K, Yokoi C, Yanase M, Akiyama J, Uemura N. Impact of INR monitoring, reversal agent use, heparin bridging, and anticoagulant interruption on rebleeding and thromboembolism in acute gastrointestinal bleeding. PLoS One. 2017 Sep 1;12(9):e0183423. doi: 10.1371/journal.pone.0183423. PMID: 28863196; PMCID: PMC5580916.

Nagata N, Yasunaga H, Matsui H, Fushimi K, Watanabe K, Akiyama J, Uemura N, Niikura R. Therapeutic endoscopy-related GI bleeding and thromboembolic events in patients using warfarin or direct oral anticoagulants: results from a large nationwide database analysis. Gut. 2018 Oct;67(10):1805-1812. doi: 10.1136/gutjnl-2017-313999. Epub 2017 Sep 5. PMID: 28874418; PMCID: PMC6145295.

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Jul 11;70(2):252-289. doi: 10.1016/j.jacc.2017.03.011. Epub 2017 Mar 15. PMID: 28315732.

Oakland K, Guy R, Uberoi R, Hogg R, Mortensen N, Murphy MF, Jairath V; UK Lower GI Bleeding Collaborative. Acute lower GI bleeding in the UK: patient characteristics, interventions and outcomes in the first nationwide audit. Gut. 2018 Apr;67(4):654-662. doi: 10.1136/gutjnl-2016-313428. Epub 2017 Feb 1. PMID: 28148540.

Oakland K, Kothiwale S, Forehand T, Jackson E, Bucknall C, Sey MSL, Singh S, Jairath V, Perlin J. External Validation of the Oakland Score to Assess Safe Hospital Discharge Among Adult Patients With Acute Lower Gastrointestinal Bleeding in the US. JAMA Netw Open. 2020 Jul 1;3(7):e209630. doi: 10.1001/jamanetworkopen.2020.9630. PMID: 32633766; PMCID: PMC7341175.

Olier I, Sirker A, Hildick-Smith DJR, Kinnaird T, Ludman P, de Belder MA, Baumbach A, Byrne J, Rashid M, Curzen N, Mamas MA; British Cardiovascular Intervention Society and the National Institute for Cardiovascular Outcomes Research. Association of different antiplatelet therapies with mortality after primary percutaneous coronary intervention. Heart. 2018 Oct;104(20):1683-1690. doi: 10.1136/heartjnl-2017-312366. Epub 2018 Feb 2. PMID: 29437885.

Ono S, Ishikawa M, Matsuda K, Tsuda M, Yamamoto K, Shimizu Y, Sakamoto N. Clinical impact of the perioperative management of oral anticoagulants in bleeding after colonic endoscopic mucosal resection. BMC Gastroenterol. 2019 Dec 2;19(1):206. doi: 10.1186/s12876-019-1124-8. PMID: 31791254; PMCID: PMC6889536.

Oscarsson A, Gupta A, Fredrikson M, Järhult J, Nyström M, Pettersson E, Darvish B, Krook H, Swahn E, Eintrei C. To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial. Br J Anaesth. 2010 Mar;104(3):305-12. doi: 10.1093/bja/aeq003. PMID: 20150346.

Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, Toly C. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021 Feb 2;143(5):e72-e227. doi: 10.1161/CIR.0000000000000923. Epub 2020 Dec 17. Erratum in: Circulation. 2021 Feb 2;143(5):e229. Erratum in: Circulation. 2023 Aug 22;148(8):e8. PMID: 33332150.

Passaglia LG, de Barros GM, de Sousa MR. Early postoperative bridging anticoagulation after mechanical heart valve replacement: a systematic review and meta-analysis. J Thromb Haemost. 2015 Sep;13(9):1557-67. doi: 10.1111/jth.13047. Epub 2015 Jul 29. PMID: 26178802.

Piran S, Khatib R, Schulman S, Majeed A, Holbrook A, Witt DM, Wiercioch W, Schünemann HJ, Nieuwlaat R. Management of direct factor Xa inhibitor-related major bleeding with prothrombin complex concentrate: a meta-analysis. Blood Adv. 2019 Jan 22;3(2):158-167. doi: 10.1182/bloodadvances.2018024133. PMID: 30658963; PMCID: PMC6341194.

Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kam CW, Kamphuisen PW, Kreuzer J, Levy JH, Royle G, Sellke FW, Stangier J, Steiner T, Verhamme P, Wang B, Young L, Weitz JI. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017 Aug 3;377(5):431-441. doi: 10.1056/NEJMoa1707278. Epub 2017 Jul 11. PMID: 28693366.

Qureshi W, Mittal C, Patsias I, Garikapati K, Kuchipudi A, Cheema G, Elbatta M, Alirhayim Z, Khalid F. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. Am J Cardiol. 2014 Feb 15;113(4):662-8. doi: 10.1016/j.amjcard.2013.10.044. Epub 2013 Nov 23. Erratum in: Am J Cardiol. 2015 Jul 1;116(1):166. PMID: 24355310.

Radaelli F, Dentali F, Repici A, Amato A, Paggi S, Rondonotti E, Dumonceau JM. Management of anticoagulation in patients with acute gastrointestinal bleeding. Dig Liver Dis. 2015 Aug;47(8):621-7. doi: 10.1016/j.dld.2015.03.029. Epub 2015 Apr 13. PMID: 25935464.

Rubin TA, Murdoch M, Nelson DB. Acute GI bleeding in the setting of supratherapeutic international normalized ratio in patients taking warfarin: endoscopic diagnosis, clinical management, and outcomes. Gastrointest Endosc. 2003 Sep;58(3):369-73. PMID: 14528210.

Shingina A, Barkun AN, Razzaghi A, Martel M, Bardou M, Gralnek I; RUGBE Investigators. Systematic review: the presenting international normalised ratio (INR) as a predictor of outcome in patients with upper nonvariceal gastrointestinal bleeding. Aliment Pharmacol Ther. 2011 May;33(9):1010-8. doi: 10.1111/j.1365-2036.2011.04618.x. Epub 2011 Mar 8. PMID: 21385193.

Schulman S, Carrier M, Lee AY, Shivakumar S, Blostein M, Spencer FA, Solymoss S, Barty R, Wang G, Heddle N, Douketis JD; Periop Dabigatran Study Group. Perioperative Management of Dabigatran: A Prospective Cohort Study. Circulation. 2015 Jul 21;132(3):167-73. doi: 10.1161/CIRCULATIONAHA.115.015688. Epub 2015 May 12. PMID: 25966905.

Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, Richardt G, Liebetrau C, Witzenbichler B, Antoniucci D, Akin I, Bott-Flügel L, Fischer M, Landmesser U, Katus HA, Sibbing D, Seyfarth M, Janisch M, Boncompagni D, Hilz R, Rottbauer W, Okrojek R, Möllmann H, Hochholzer W, Migliorini A, Cassese S, Mollo P, Xhepa E, Kufner S, Strehle A, Leggewie S, Allali A, Ndrepepa G, Schühlen H, Angiolillo DJ, Hamm CW, Hapfelmeier A, Tölg R, Trenk D, Schunkert H, Laugwitz KL, Kastrati A; ISAR-REACT 5 Trial Investigators. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. N Engl J Med. 2019 Oct 17;381(16):1524-1534. doi: 10.1056/NEJMoa1908973. Epub 2019 Sep 1. PMID: 31475799.

Scott MJ, Veitch A, Thachil J. Reintroduction of anti-thrombotic therapy after a gastrointestinal haemorrhage: if and when? Br J Haematol. 2017 Apr;177(2):185-197. doi: 10.1111/bjh.14599. Epub 2017 Mar 8. PMID: 28272736.

197 Sung JJ, Lau JY, Ching JY, Wu JC, Lee YT, Chiu PW, Leung VK, Wong VW, Chan FK. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. Ann Intern Med. 2010 Jan 5;152(1):1-9. doi: 10.7326/0003-4819-152-1-201001050-00179. Epub 2009 Nov 30. PMID: 19949136.

Siau K, Hannah JL, Hodson J, Widlak M, Bhala N, Iqbal TH. Stopping antithrombotic therapy after acute upper gastrointestinal bleeding is associated with reduced survival. Postgrad Med J. 2018 Mar;94(1109):137-142. doi: 10.1136/postgradmedj-2017-135276. Epub 2017 Nov 3. PMID: 29101296.

Sengupta N, Feuerstein JD, Patwardhan VR, Tapper EB, Ketwaroo GA, Thaker AM, Leffler DA. The risks of thromboembolism vs. recurrent gastrointestinal bleeding after interruption of systemic anticoagulation in hospitalized inpatients with gastrointestinal bleeding: a prospective study. Am J Gastroenterol. 2015 Feb;110(2):328-35. doi: 10.1038/ajg.2014.398. Epub 2014 Dec 16. Erratum in: Am J Gastroenterol. 2015 Mar;110(3):480. PMID: 25512338.

Smith MN, Deloney L, Carter C, Weant KA, Eriksson EA. Safety, efficacy, and cost of four-factor prothrombin complex concentrate (4F-PCC) in patients with factor Xa inhibitor-related bleeding: a retrospective study. J Thromb Thrombolysis. 2019 Aug;48(2):250-255. doi: 10.1007/s11239-019-01846-5. PMID: 30941571.

Spyropoulos AC, Turpie AG, Dunn AS, Kaatz S, Douketis J, Jacobson A, Petersen H; REGIMEN Investigators. Perioperative bridging therapy with unfractionated heparin or low-molecular-weight heparin in patients with mechanical prosthetic heart valves on long-term oral anticoagulants (from the REGIMEN Registry). Am J Cardiol. 2008 Oct 1;102(7):883-9. doi: 10.1016/j.amjcard.2008.05.042. Epub 2008 Jul 31. PMID: 18805116.

Staerk L, Lip GY, Olesen JB, Fosbøl EL, Pallisgaard JL, Bonde AN, Gundlund A, Lindhardt TB, Hansen ML, Torp-Pedersen C, Gislason GH. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. BMJ. 2015 Nov 16;351:h5876. doi: 10.1136/bmj.h5876. PMID: 26572685; PMCID: PMC4646074.

Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbüchel H; ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018 Apr 21;39(16):1330-1393. doi: 10.1093/eurheartj/ehy136. PMID: 29562325.

Strate LL, Orav EJ, Syngal S. Early predictors of severity in acute lower intestinal tract bleeding. Arch Intern Med. 2003 Apr 14;163(7):838-43. doi: 10.1001/archinte.163.7.838. PMID: 12695275.

Tapaskar N, Pang A, Werner DA, Sengupta N. Resuming Anticoagulation Following Hospitalization for Gastrointestinal Bleeding Is Associated with Reduced Thromboembolic Events and Improved Mortality: Results from a Systematic Review and Meta-Analysis. Dig Dis Sci. 2021 Feb;66(2):554-566. doi: 10.1007/s10620-020-06248-9. Epub 2020 Apr 11. PMID: 32279174.

Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, Florido R, Gluckman TJ, Hucker WJ, Mehran R, Messé SR, Perino AC, Rodriguez F, Sarode R, Siegal DM, Wiggins BS. 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2020 Aug 4;76(5):594-622. doi: 10.1016/j.jacc.2020.04.053. Epub 2020 Jul 14. Erratum in: J Am Coll Cardiol. 2021 Jun 1;77(21):2760. PMID: 32680646.

Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, Lipiecki J, Richardt G, Iñiguez A, Brunel P, Valdes-Chavarri M, Garot P, Talwar S, Berland J, Abdellaoui M, Eberli F, Oldroyd K, Zambahari R, Gregson J, Greene S, Stoll HP, Morice MC; LEADERS FREE Investigators. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. N Engl J Med. 2015 Nov 19;373(21):2038-47. doi: 10.1056/NEJMoa1503943. Epub 2015 Oct 14. PMID: 26466021.

Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018 Jan 14;39(3):213-260. doi: 10.1093/eurheartj/ehx419. PMID: 28886622.

Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrié D, Hovasse T, Garot P, El Mahmoud R, Spaulding C, Helft G, Diaz Fernandez JF, Brugaletta S, Pinar-Bermudez E, Mauri Ferre J, Commeau P, Teiger E, Bogaerts K, Sabate M, Morice MC, Sinnaeve PR; SENIOR investigators. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. Lancet. 2018 Jan 6;391(10115):41-50. doi: 10.1016/S0140-6736(17)32713-7. Epub 2017 Nov 1. PMID: 29102362.

Veitch AM, Vanbiervliet G, Gershlick AH, Boustiere C, Baglin TP, Smith LA, Radaelli F, Knight E, Gralnek IM, Hassan C, Dumonceau JM. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. Endoscopy. 2016 Apr;48(4):385-402. doi: 10.1055/s-0042-102652. Epub 2016 Feb 18. Erratum in: Endoscopy. 2016 Apr;48(4):c1. PMID: 26890676.

Veitch AM, Radaelli F, Alikhan R, Dumonceau JM, Eaton D, Jerrome J, Lester W, Nylander D, Thoufeeq M, Vanbiervliet G, Wilkinson JR, Van Hooft JE. Endoscopy in patients on antiplatelet or anticoagulant therapy: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guideline update. Gut. 2021 Sep;70(9):1611-1628. doi: 10.1136/gutjnl-2021-325184. PMID: 34362780; PMCID: PMC8355884.

Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, Hata Y, Yagi M, Suematsu N, Yokomatsu T, Takamisawa I, Doi M, Noda T, Okayama H, Seino Y, Tada T, Sakamoto H, Hibi K, Abe M, Kawai K, Nakao K, Ando K, Tanabe K, Ikari Y, Hanaoka KI, Morino Y, Kozuma K, Kadota K, Furukawa Y, Nakagawa Y, Kimura T; STOPDAPT-2 Investigators. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. JAMA. 2019 Jun 25;321(24):2414-2427. doi: 10.1001/jama.2019.8145. PMID: 31237644; PMCID: PMC6593641.

Witt DM, Delate T, Garcia DA, Clark NP, Hylek EM, Ageno W, Dentali F, Crowther MA. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. Arch Intern Med. 2012 Oct 22;172(19):1484-91. doi: 10.1001/archinternmed.2012.4261. PMID: 22987143.

Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H; AFIRE Investigators. Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. N Engl J Med. 2019 Sep 19;381(12):1103-1113. doi: 10.1056/NEJMoa1904143. Epub 2019 Sep 2. Erratum in: N Engl J Med. 2021 Oct 21;385(17):1632. PMID: 31475793.

Bijlagen bij module periprocedureel beleid bij endoscopie

Tabel 1. Bloedingsrisico per type ingreep

Laag-risico	Hoog-risico
• Poliepectomie (kleine poliepen, <10 mm) • Diagnostische endoscopie (gastroscopie, sigmoïdoscopie, colonoscopie, ballon-geassisteerde enteroscopie) inclusief biopten* • Endoscopische Retrograde Cholangiopancreaticografie (ERCP) met endoprothese zonder papillotomie • Endo-echografie (EUS) zonder interventie • Video capsule endoscopie • Stentplaatsing (zonder dilatatie) • Inbrengen voedingssonde • Rubberbandligatie bij slokdarmvarices en hemorroïden	• Poliepectomie (grote poliepen of colonoscopie uitgevoerd in het kader van het bevolkingsonderzoek* • Mucosaresectie (EMR) / submucosale dissectie (ESD) / intermusculaire dissectie (EID) • Endoscopische Full Thickness Resectie (EFTR) • Perorale endoscopische myotomie • 'Submucosal tunneling' endoscopische resectie • Papillotomie (biliair of pancreas) • Ampullectomie • Dilatatie • PEG-plaatsing • EUS met interventie (bijv. FNA/LAMS/etc) • Leverbiopsie • Therapeutische enteroscopie • Endoscopische coagulatie • Barrett endotherapie (bijv. RFA) • Klieven Zenkers divertikel • Vacuümtherapie

*** vanwege de hoge kans op poliepectomie (>65%) is een colonoscopie in het kader van het bevolkingsonderzoek te beschouwen als een therapeutische colonoscopie. EMR: Endoscopische Mucosaresectie, ESD: Endoscopische submucosale dissectie, EID: endoscopische intermusculaire dissectie, EFTR: Endoscopische Full Thickness Resectie, ERCP: Endoscopische Retrograde Cholangiopancreaticografie, EUS: Endo-echografie, FNA: Fine-needle aspiratie, LAMS: lumen apposing metal stent, PEG: Percutane endoscopische gastrostomie, RFA: Radiofrequente ablatie**

Tabel 2. Risico op trombo-embolische gebeurtenissen bij 1) arteriële indicatie voor antistolling gebruik 2) antistolling gebruik vanwege een doorgemaakte VTE *

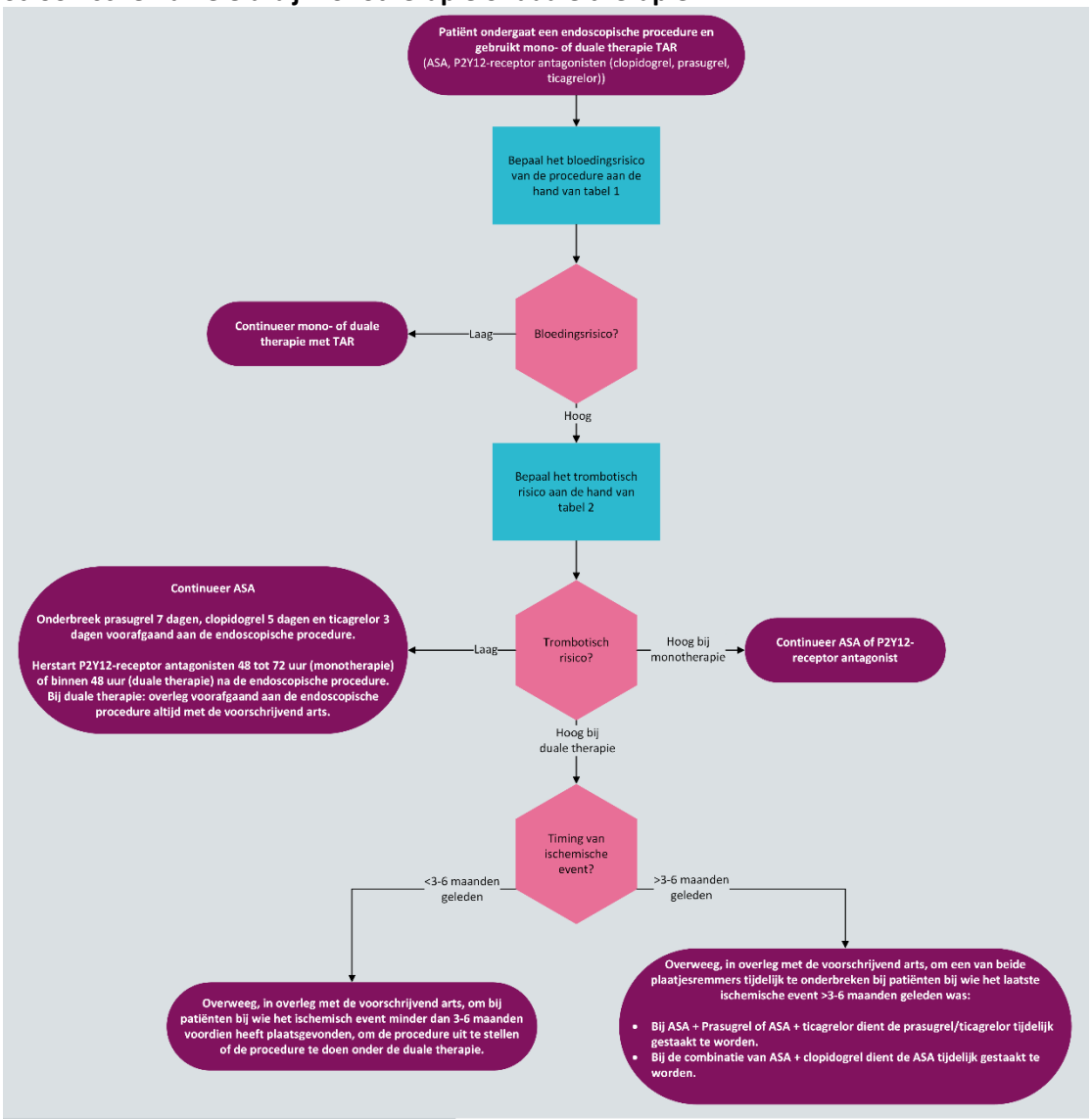
1)Trombo-embolie risico bij een arteriële indicatie voor antistolling gebruik	
Laag-risico (jaarlijks < 10%)	**Hoog-risico (jaarlijks > 10 %)**
• Geïsoleerd atriumfibrilleren, CHA_2DS_2-VASc: 0 tot 7 en geen recent (< 6 maanden) herseninfarct/TIA • Mechanische hartklep in aortapositie > 3 maanden geleden geplaatst zonder extra risicofactor * • Bioklep > 3 maanden geleden geplaatst • Recidiverend herseninfarct/TIA zonder additionele hoog risicofactor cardiale emboliebron (atriumfibrilleren, symptomatische, significante ACI stenose, antifosfolipidensyndroom) • Eenmalig herseninfarct/TIA	• Geïsoleerd atriumfibrilleren, zonder klepgebrek, met CHA_2DS_2-VASc: 8 tot 9 • Geïsoleerd atriumfibrilleren met reumatische hartziekte • Atriumfibrilleren met mechanische hartklep • Atriumfibrilleren met recent (< 6 maanden) herseninfarct/TIA ongeacht de CHA_2DS_2-VASc-score • Bij biokleppen (inclusief TAVI) < 3 maanden geleden geplaatst, alleen op indicatie van de operateur • Mechanische hartklep in mitralis, tricuspidalis of pulmonalis positie • Aortamechanoprothesen met extra risicofactor in overleg met de operateur • Hartklepprothese (inclusief bioklep) met extra risicofactor[≠] • Mechanische hartklep oud model: caged ball, tilting disc (Starr-Edwards, Björk-Shiley) • Intracardiale trombus • Recidiverend herseninfarct/TIA bij symptomatische ACI stenose • Chronische trombo-embolische pulmonale hypertensie[#]

2) Trombo-embolie risico bij antistolling gebruik met doorgemaakte VTE	
Laag-risico (1 maand risico < 10%)	**Hoog-risico (1 maand risico > 10%)**
• ≥ 3 maanden na initiële VTE • > 3 maanden na eerste of recidief VTE en geen recidief onder antistolling	• < 3 maanden na initiële VTE • Recidief VTE onder stabiele antistolling (> 1 maand) • Recidief VTE bij eerdere tijdelijke onderbreking van antistolling (ook > 3 maanden na laatste VTE)

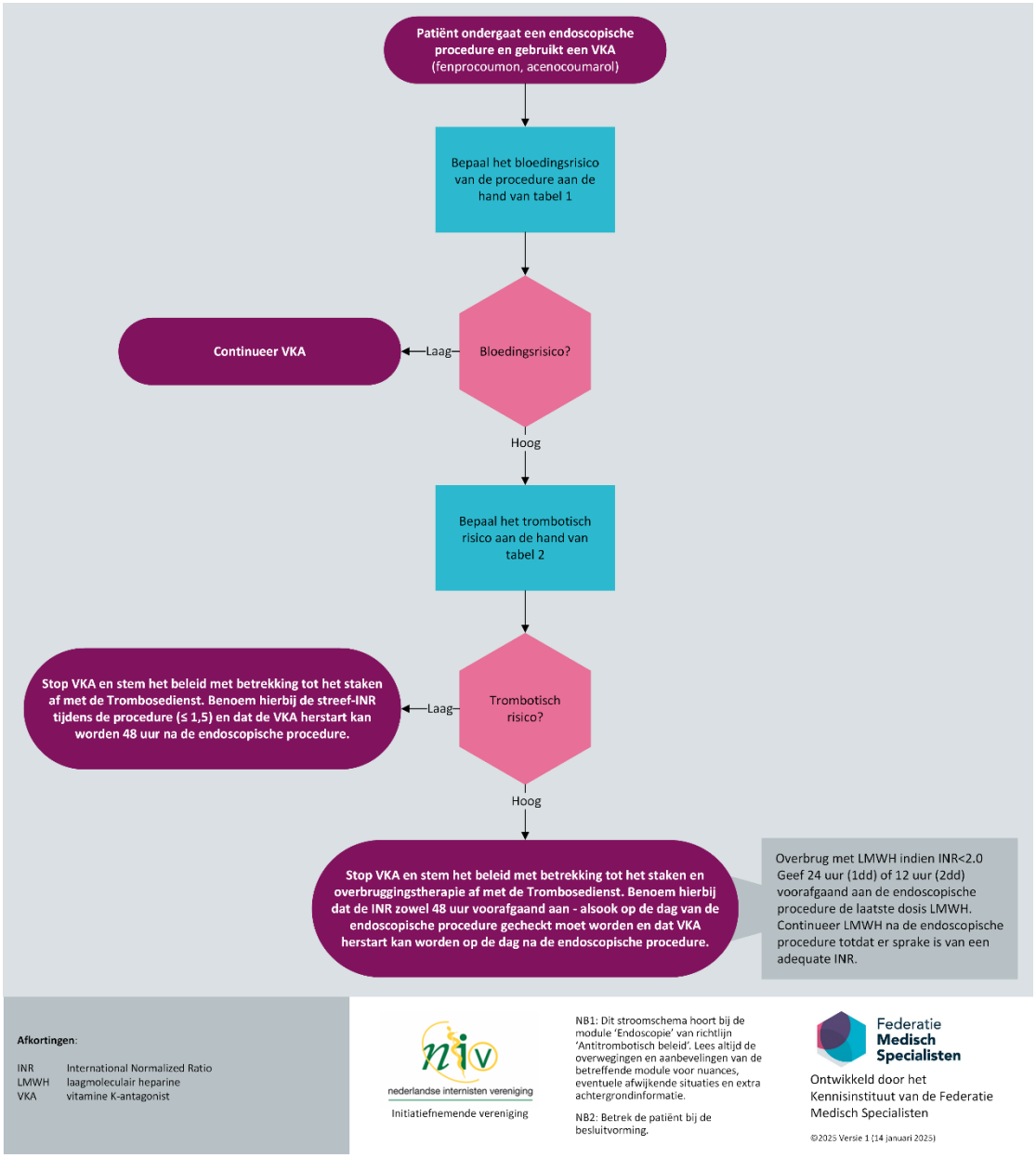
***De module periprocedureel beleid wordt momenteel herzien. Bij deze herziening wordt er ook gekeken naar deze tabel, en wordt onder andere deze tabel aangevuld met specificaties voor patienten op duale therapie trombocytenaggregatieremmers.**

[≠] Risicofactoren zijn: atriumfibrilleren, linker ventrikel ejectiefractie< 35%, voorgeschiedenis van trombo-embolie. #Dit betreft patiënten met aangetoonde CTEPH die nog geen pulmonalis endarterectomie hebben ondergaan, of waarbij de pulmonalis endarterectomie niet tot normalisatie van de drukken heeft geleid. Patiënten in de chronisch stabiele fase van de ziekte na een succesvolle pulmonalis endarterectomie vallen in de laag risico categorie. TIA: transient ischemic attack; TAVI: Transcatheter Aortic Valve Implantation; VTE: Veneuze Trombo-Embolie; ACI: arteria carotis interna

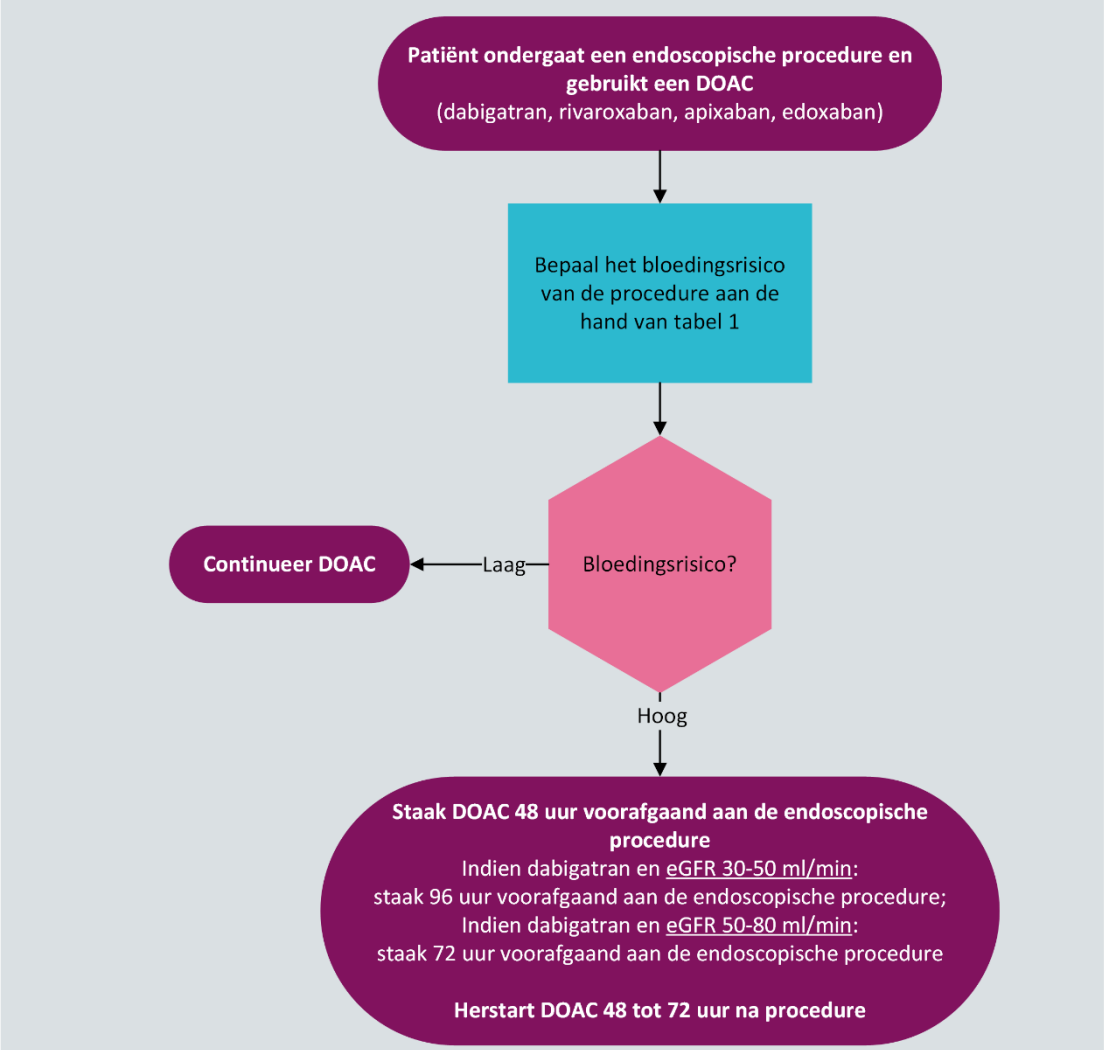
Stroomschema Beleid bij monotherapie of duale therapie TAR



Stroomschema Beleid bij behandeling met VKA



Stroomschema Beleid bij behandeling met DOAC



nederlandse internisten vereniging

Initiatiefnemende vereniging

NB1: Dit stroomschema hoort bij de module 'Endoscopie' van richtlijn 'Antitrombotisch beleid'. Lees altijd de overwegingen en aanbevelingen van de betreffende module voor nuances, eventuele afwijkende situaties en extra achtergrondinformatie.

NB2: Betrek de patiënt bij de besluitvorming.

Federatie Medisch Specialisten

Ontwikkeld door het Kennisinstituut van de Federatie Medisch Specialisten

Implementatieplan

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

15

(Sub)aanbeveling	**Sterkte van de aanbeveling**	**Bewijskracht per uitkomstmaat**	**Verkeerslicht per (sub)aanbeveling**
Aanbeveling 1: **<u>Algemene aanbevelingen</u>** Bespreek met de patiënt het trombotisch risico als gevolg van het staken van de antitrombotica alsook het bloedingsrisico bij het continueren van de antitrombotica. Bepaal het bloedingsrisico van de endoscopische procedure. Maak hierbij gebruik van Tabel 1. Bepaal het trombo-embolisch risico, indien er sprake is van een hoog bloedingsrisico. Maak hierbij gebruik van Tabel 2. Overleg bij patiënten met een hoog bloedingsrisico én een hoog trombo-embolisch risico met de voorschrijver van de antitrombotica om tot een gewogen besluit te komen.	**X** Sterk (doe/ gebruik) / □ Zwak (overweeg)	**Overall bewijskracht** □ **H** □ **M** □ **L** □ **VL** □ **NG** **Range bewijskracht van alle uitkomstmaten** □ **H** □ **M** □ **L** □ **VL** □ **NG** **OF** **X voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in □ **ORANJE:** gebruik tabel B **X LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in
Aanbeveling 2: **<u>Patiënten met monotherapie trombocytenaggregatieremmers (TAR)</u>**	**X** Sterk (doe/ gebruik) / □ Zwak (overweeg)	**Overall bewijskracht** □ **H** □ **M** □ **L** □ **VL** □ **NG** **Range bewijskracht van alle uitkomstmaten** □ **H** □ **M** □ **L** □ **VL** □ **NG**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in □ **ORANJE:** gebruik tabel B

Laag bloedingsrisico Continueer salicylzuur/carbasalaatcalcium (ASA) en/of clopidogrel/ticagrelor/prasugrel (P2Y12 receptor antagonist) bij patiënten die een endoscopische procedure met een laag bloedingsrisico ondergaan. *Hoog bloedingsrisico en laag trombotisch risico* Continueer acetylsalicylzuur/carbasalaatcalcium (ASA) bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan en waarbij sprake is van een laag trombotisch risico. Onderbreek de P2Y12-receptor antagonist (prasugrel 7 dagen, clopidogrel 5 dagen en ticagrelor 3 dagen voorafgaand aan de endoscopie bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan en waarbij er sprake is van een laag trombotisch risico. Herstart P2Y12 receptor antagonist na 48 tot 72 uur. *Hoog bloedingsrisico en hoog trombotisch risico* Continueer de ASA of de P2Y12-receptor antagonist bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan en waarbij sprake is van een hoog trombotisch risico. **<u>Patiënten met duale therapie trombocytenaggregatieremmers (TAR)</u>**		**OF** **X voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	**X LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in

Overleg voorafgaand aan de endoscopische procedure altijd met de voorschrijvend arts over het beleid van eventueel tijdelijk staken van de een van de TARs van de duale therapie. *Laag bloedingsrisico* Continueer salicylzuur/carbasalaatcalcium (ASA) en clopidogrel/ticagrelor/prasugrel (P2Y12 receptor antagonist) bij patiënten die een endoscopische procedure met een laag bloedingsrisico ondergaan. *Hoog bloedingsrisico en laag trombotisch risico* Onderbreek de P2Y12 receptor antagonist (prasugrel 7 dagen preoperatief, clopidogrel 5 dagen preoperatief en ticagrelor 3 dagen preoperatief) bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan en waarbij sprake is van een laag trombotisch risico. Continueer de ASA. Herstart P2Y12 receptor antagonisten binnen 48 uur na de endoscopische procedure. *Hoog bloedingsrisico en hoog trombotisch risico* Overweeg, in overleg met de voorschrijvend arts om een van de TAR's tijdelijk te onderbreken bij patiënten die 3-6 maanden duale therapie hebben ontvangen en waarbij er geen ischemisch event is opgetreden. Herstart duale therapie binnen 48 uur na de endoscopische procedure.			

Herstarten algemeen Herstart ASA/clopidogrel/ticagrelor /prasugrel of een andere plaatjesremmer na de endoscopische procedure met de dosis, die past bij het voorgeschreven middel. Volg hierbij de stappen uit het stroomschema 'Beleid bij monotherapie of duale therapie TAR'.			
Aanbeveling 3: **<u>Vitamine K-antagonisten (VKA)</u>** ***Laag bloedingsrisico*** Continueer VKA bij patiënten die een endoscopische procedure met een laag bloedingsrisico ondergaan. ***Hoog bloedingsrisico en laag trombotisch risico*** Stop VKA bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan en waarbij sprake is van een laag trombotisch risico en stem het beleid met betrekking tot het staken af met de Trombosedienst en benoem hierbij: - Dat de streef-INR ≤ 1,5 is; - Dat de VKA herstart kan worden 48 uur na de endoscopische procedure, met 1.5-2 maal de gebruikelijke dagelijkse dosis. ***Hoog bloedingsrisico en hoog trombotisch risico*** Stop VKA bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan	**X** Sterk (doe/ gebruik) / □ Zwak (overweeg)	**Overall bewijskracht** □ **H** □ **M** □ **L** □ **VL** □ **NG** **Range bewijskracht van alle uitkomstmaten** □ **H** □ **M** □ **L** □ **VL** □ **NG** **OF** **X voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in □ **ORANJE:** gebruik tabel B **X LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in

en waarbij sprake is van een hoog trombotisch risico. Stem het beleid met betrekking tot staken en de overbruggingstherapie af met de Trombosedienst. Benoem hierbij: - Dat de INR 48 uur voorafgaand aan de endoscopische procedure gecheckt moet worden; o Start met een therapeutische dosis LMWH, indien INR <2.0. Geef 24 uur (1dd) of 12 uur (2dd) voorafgaand aan de endoscopische ingreep de laatste dosis. o Indien er gebruik wordt gemaakt van ongefractioneerde heparine, staak de toediening via het infuus vier uur voorafgaand aan			

de endoscopische procedure. - Dat de INR op de dag van de endoscopische procedure gecheckt moet worden, waarbij de streef-INR ≤1,5 is; - Dat de VKA herstart kan worden op de dag na de endoscopische procedure. *Herstarten LMWH* - Geef een profylactische dosis LMWH, zolang er geen therapeutische LMWH wordt herstart. - Herstart de therapeutische LMWH tenminste 48 uur na de endoscopische procedure. - De LMWH kan worden gestaakt indien de INR eenmaal boven 2.0 (indien de streefwaarde 2,0 tot 3,0 is) of 2,5 (indien de streefwaarde 2,5 tot 3,5 is). Volg hierbij de stappen uit het stroomschema 'Beleid bij behandeling met VKA'.			

Aanbeveling 4: **<u>Directe Orale Anticoagulantia (DOAC)</u>** ***Laag bloedingsrisico*** Continueer DOAC bij patiënten die een endoscopische procedure met een laag bloedingsrisico ondergaan. ***Hoog bloedingsrisico*** Onderbreek de DOACs bij patiënten die een endoscopische procedure met een hoog bloedingsrisico ondergaan, afhankelijk van het type DOAC en de nierfunctie: - Xa-remmers: 48 uur voorafgaand aan de procedure; - Dabigatran en eGFR >80 ml/min: 48 uur voorafgaand aan de procedure; - Dabigatran en eGFR 50-80 ml/min: 72 uur voorafgaand aan de ingreep; - Dabigatran en eGFR 30-50 ml/min: 96 uur voorafgaand aan de procedure. Herstart de DOACs 48 uur na de endoscopische procedure bij een hoog trombotisch risico en 72 uur na de endoscopische procedure bij een laag trombotisch risico. Volg hierbij de stappen uit het stroomschema 'Beleid bij behandeling met DOAC'.	**X** Sterk (doe/ gebruik) / □ Zwak (overweeg)	**Overall bewijskracht** □ **H** □ **M** □ **L** □ **VL** □ **NG** **Range bewijskracht van alle uitkomstmaten** □ **H** □ **M** □ **L** □ **VL** □ **NG** **OF** **X voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in □ **ORANJE:** gebruik tabel B **X LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in

Implementatietabel

Zie aanbevelingen hierboven – deze tabel geldt voor alle aanbevelingen			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	☐ **Ongewenste praktijkvariatie** ☐ **Nieuwe evidentie** **X Anders** **Toelichting:** Men had het idee dat de overkoepelende modules over periprocedureel beleid niet voldoende handvaten gaven voor periprocedureel beleid rondom endoscopische ingrepen en dat daarmee de NVMDL-richtlijn uit 2016 niet vervangen kon worden.		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	☐ < **1000** ☐ < **5000** **X 5000-40.000** ☐ **> 40.000**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	**X Ja**: hoe verhoudt deze aanbeveling zich tot de andere aanbevelingen uit deze module/ richtlijn of uit andere richtlijnen(modules)? Dient hier rekening mee gehouden te worden bij de implementatie of kan dit worden gezien als een losstaande aanbeveling? **Toelichting:** de modules maken onderdeel uit van de totale set van modules over periprocedureel beleid. ☐ **Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*		De module maakt onderdeel uit van de set modules over periprocedureel beleid. Daarnaast wordt ook de overkoepelende module over periprocedureel herzien, wat

			t.z.t. ook zal zorgen voor meer aandacht voor de modules over periprocedureel beleid en daarop aansluitend de LTA-Antistollingszorg.
b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	Onvoldoende kennis over de nieuwe aanbevelingen.	De andere modules over periprocedureel beleid zijn al langere tijd beschikbaar en zijn naar verwachting ook bekend onder de zorgverleners.
c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	Het is voor patiënten niet altijd duidelijk wie bijvoorbeeld het aanspreekpunt is voor het periprocedurele beleid en hoe het opgevolgd wordt.	De module over informatievoorziening en de overkoepelende module over periprocedureel beleid worden herzien. Hierin wordt aandacht gegeven aan de vragen die er leven bij de patiënt.
d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*		
e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	Een deel van de endoscopieën wordt uitgevoerd in het kader van het bevolkingsonderzoek.	De modules over periprocedureel beleid bestaan al sinds 2021 en worden veel gebruikt. Deze module met specifieke aanbevelingen voor endoscopische ingrepen sluit naar verwachting goed aan bij de klinische praktijk.

f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*		

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	**X** Patiënt/ cliënt (naaste) **X** Professional **X** Beroepsvereniging ☐ Ziekenhuis(bestuurder) ☐ Zorgverzekeraars/ NZa ☐ Zorginstituut [duiding nodig] ☐ Lokale stollingscommissies
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	De modules over periprocedureel beleid bestaan al sinds 2021 en worden veel gebruikt. Betrokken zorgverleners dienen door hun beroepsvereniging op de hoogte te worden gesteld van de nieuwe aanbevelingen over het beleid m.b.t. endoscopische ingrepen. Daarnaast kan het helpend zijn als de aanbevelingen worden besproken in bijv. vakgroepvergaderingen en lokale werkgroepen. Lokale stollingscommissies kunnen hier ook een rol in spelen. Waar relevant dienen e-learnings te worden aangepast. Tot slot zal (lokale) patiënteninformatie aangepast moeten worden.
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X** < 1 jaar **X** < 2 jaar ☐ < 3 jaar De modules over periprocedureel beleid bestaan al sinds 2021 en worden veel gebruikt. De verwachting is daarnaast dat de aanbevelingen goed aansluiten bij de klinische praktijk en de implementatie daarom ook niet lang zal hoeven duren.
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	☐ **Ja* X Nee** **Toelichting:** De module zal onderdeel uit gaan maken van een set modules over periprocedureel beleid. Daar is al veel aandacht bijv. ook in de LTA-antistollingszorg. Er is geen specifieke aandacht nodig voor deze specifieke module over periprocedureel beleid bij endoscopische ingrepen.

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

Evidence tables

n.v.t.

Table of excluded studies

n.v.t.

Literature search strategy

n.v.t.

Module 9 Herstarten antistollingstherapie na bloeding

Autorisatie en geldigheid

Autorisatiedatum:	*pending*
Eerstvolgende beoordeling actualiteit	volgende cyclus binnen het cluster Antitrombotisch beleid
Geautoriseerd door:	*pending*
Belangrijkste wijzigingen t.o.v. vorige versie:	de overwegingen en aanbevelingen zijn verder aangescherpt. Er worden concretere handvaten gegeven.
Herbevestiging:	n.v.t.
Regiehouder:	Nederlandse Internisten Vereniging

Uitgangsvraag

Hoe moeten we omgaan met het herstarten van antistollingstherapie na een bloeding?

Introduction

It is a dilemma if and when to restart anticoagulation treatment in patients with anticoagulation-associated bleeding (i.e. intracranial, gastro-intestinal, other). The risks of both recurrent bleeding and a thromboembolic event must be considered. Especially in the absence of clear (contra-) indications, the decision depends on various patient-related factors.

Search and select

A systematic review of the literature was performed to answer the following question: what are the (un)favorable effects of (early) restarting of anticoagulation after anticoagulation-associated major bleeding (intracerebral, gastrointestinal or other) in adult patients, compared to no/delayed restarting anticoagulation?

P	**(Patients)**	adults with anticoagulation-associated major bleeding (intracerebral, gastrointestinal, or other)
I	**(Intervention)**	(early) restart of anticoagulation
C	**(Comparison)**	delayed or no restart of anticoagulation
O	**(Outcomes)**	recurrent major bleeding, mortality, thrombo-embolic event (arterial and venous)

<u>Relevant outcome measures</u>

The guideline development group considered mortality and recurrent major bleeding as critical outcome measures for decision-making, and thrombo-embolic events as an important outcome measure for decision-making.

The working group defined the outcome measures as follows:

- Major bleeding: fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin levels of 1.24 mmol/L (20 g/L or greater) or more, or leading to a

transfusion of 2 U or more of whole blood or red cells, as defined by the International Society of Thrombosis and Haemostasis.

A priori, the working group did not define the other outcome measures listed above but used the definitions used in the studies.

The working group defined a risk difference of 3%* as a minimal clinically (patient) important difference for mortality, venous thromboembolism, thromboembolic complications and major bleeding.
**Based on the differences applied in the guidelines on thromboprophylaxis in patients with COVID-19. This working group derived the minimal clinically (patient) important differences from the ACCP (2012).*

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms. The initial search was performed in 2016. The detailed search strategy is depicted under the tab Methods. The search included studies published in English or Dutch in 2010 or later. The systematic literature search resulted in 196 hits. Studies were selected based on the following criteria: observational studies (including cohort studies) performed in patients with coagulation-associated major bleedings in which restart of anticoagulation was compared with no restart. Only studies with sufficient data representation were selected. Based on title and abstract 11 studies were initially selected. After screening of the full-text, five studies were excluded (see Table excluded studies). Six studies were included.

An updated search was performed on March 13th 2024. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 1,215 hits. Studies were selected based on the following criteria: systematic reviews/meta-analysis of RCT's or cohort studies (published in 2020 or later), RCT's and cohort studies of sufficient size (N>500), in which restart of anticoagulation was compared with no or delayed restart of anticoagulation, in adults with anticoagulation-associated major bleeding (intracerebral, gastrointestinal or other).
ASReview was used for the selection of relevant articles. ASReview uses state-of-the-art active learning techniques to select the most relevant articles from a large number of potential hits. The first step is to indicate priors. A prior is an article that is found in the current number of hits and complies (or best matches) to the current selection criteria. The standard (default) model specifications were used for the screening for these papers. 43 studies were initially selected based on title and abstract screening using ASReview. After screening of the full-text, 36 studies were excluded (see exclusion table). Seven studies were included.

Results
From the initial literature search six cohort studies could be included. Since then, several RCT's were published. However, those RCT's were phase-2 trials (like Schreuder, 2021) or did not focus on patients with anticoagulation related bleeding (like Salman, 2021). So the updated search did not find (systematic reviews of) RCT's that could be included. Beforehand, it was decided that the initial literature analysis will not be updated with observational data. The working group is of the opinion that this observation data will be insufficient to provide a clear answer, i.e. the levels of evidence will remain very low. Seven cohort studies did fulfil the inclusion criteria. A concise overview of these data is provided following the initial literature analysis.

Part I: Gastro-intestinal bleedings

Summary of literature

Description of studies

Three (non-randomised) comparative studies were analyzed in which patients with anticoagulation-associated gastrointestinal bleeding were included (Witt, 2012; Sengupta, 2015; Qureshi, 2014).

Witt (2012) performed a retrospective cohort study based on information recorded in databases. Patients with a gastrointestinal bleeding during warfarin use were included. Patients are divided into two categories: (1) restart of warfarin therapy, and no restart of warfarin. The follow-up duration was 90 days. Variables about the treatment and the gastrointestinal bleeding index were collected. Kaplan-Meier curves were constructed and Cox proportional hazards modelling was performed to correct for possible confounders. A total of 442 patients were included in the study. After the index gastrointestinal bleeding, warfarin therapy was restarted for 260 patients (58.8%) (including 41 patients for whom warfarin therapy was never stopped). The average time to restart was four days (two to nine days). In the restart group, heart valve indication for warfarin, and gastrointestinal bleeding at the rectal anus (especially hemorrhoidal bleeding) was more common. Also, compared to patients who did not restart warfarin, patients who restarted were on average younger (71.8 versus 77.7 years, $p<0.001$) and the source of the gastrointestinal bleeding was more often unknown (16.9% vs 26.9%, $p=0.01$).

Sengupta (2015) performed a prospective observational cohort study on consecutive patients who were hospitalized for gastrointestinal bleeding during anticoagulant treatment. Patients were classified into two groups: patients for whom anticoagulation was restarted, and patients for whom anticoagulation was not restarted. Patients were called 90 days after discharge to collect the following outcomes: thromboembolic events, hospital readmissions related to gastrointestinal bleeding, and mortality. Univariate and adjusted Cox proportional hazards were used to map the factors associated with thrombotic events, rebleeding and mortality. A total of 197 patients were included. Anticoagulation was stopped in 76 (39%) of patients (stopping was defined as withholding anticoagulation for at least 72 hours after discharge). After excluding patients for whom anticoagulation was restarted due to a thromboembolic episode in follow-up, 15 (20%) of the 76 patients restarted anticoagulation during the 90-day follow-up period. Adjustment was performed for age, sex, Charlson comorbidity index, need for transfusion, and active malignancy.

Qureshi (2014) performed a retrospective cohort study that included patients who experienced gastrointestinal bleeding while taking anticoagulants (n=1,329). For this study, data from the database of a health insurance company (Henry Ford Health System) was used. A gastrointestinal bleeding was defined as a decrease in hemoglobin by 3.2 mmol/L, visible bleeding, or positive endoscopic evaluation. Warfarin was restarted in 653 patients (49.1%) after a median duration of 50 days. Analyses stratified for the duration of the interruption of warfarin interruption were also performed. In Caucasians, patients with simultaneously high and low digestive tract hemorrhage, diabetes, patients with renal disease, previous coronary artery disease and fall history restarted less frequently ($p<0,05$). On average, comorbidities were more common in the group that did not restart treatment. The main reasons for not restarting were physician preference (18%) and patients' inability to come to the anticoagulation clinic (19%).

All three included studies reported on the outcome measures of mortality, recurrent bleeding (GIB) and thrombotic events. The results of the studies could not be pooled due to differences in study design and differences in the factors adjusted for in the multivariate analyses.

Mortality

In the study of Witt (2012) 52 (11.8%) patients died during the 90-day follow-up period. Restarting warfarin was associated with a lower risk of death (Hazard Ratio (HR, 95%CI): 0.31 (0.15 to 0.62) in multivariable analysis adjusted for propensity score, CDS, age, sex, GIB location, ICU admission, hypertension, previous stroke, pre-GIB rate INR in range, use of LMWH, length of stay, acute GIB treatment (blood transfusion). This association persisted in post-hoc analyses in which all patients who died within one week of the first (index) GIB were excluded. The mortality ratio was lowest when warfarin was resumed between 15 and 90 days after the index GIB (2.3%). The authors indicated that this survival difference may be related to more frequent restart of warfarin in patients with a better life expectancy, despite the corrections they have made.

In the study by Sengupta (2015), a total of 16 (8%) patients died during the 90-day follow-up period. None of the deaths in this cohort was related to recurrent GIB or thrombotic events. In multivariate analysis, risk of death was lower for patients who restarted compared to those who did not restart anticoagulants (HR 0.632, 95% CI 0.216 to 1.89).

In the study by Qureshi (2014), a total of 463 patients died over a two-year period. Patients restarting warfarin had lower mortality risk (adjusted HR 0.66, 95%CI 0.55 to 0.80) compared to the group that discontinued warfarin. Adjustments were made for age, sex, ethnicity, Charlson co-morbidity index, number of blood product transfusions, INR during admission, CHADS2 and HAS-BLED scores.

Recurrent bleeding

Witt (2012) reported recurrence of GIB in 36 out of 442 patients (8.4%). Compared to the group that did not restart warfarin, a higher percentage of patients who did restart warfarin had a recurrence of GIB (10% in the restarted group vs. 5.5% in the non-restart group). Multivariate analysis, controlled for propensity score, CDS, age, sex, indication for warfarin use, diagnosis of heart failure, location GIB, pre-GIB target INR, pre-GIB percentage INR within the range, use of LMWH, duration of hospitalization, acute GIB treatment (blood transfusion) found an increased risk of recurrent bleeding with warfarin restart (HR 1.32, 95%CI 0.50 to 3.57). Compared to all other patients, patients who restarted between one and seven days after the GIB had a higher risk of recurrence of GIB (6.23% vs. 12.4%).

In the study of Sengupta (2015), 27 patients (14%) were readmitted with a recurrent GIB (mean time to admission 13 days) in the 90-day follow-up. In multivariate regression analysis, restarting anticoagulants at hospital discharge was related to a higher risk of readmission associated with recurrent GIB within 90 days (HR 2.17, 95%CI 0.861 to 6.67).

In Qureshi (2014) 90 patients developed a recurrence severe GIB within 90 days. Restarting warfarin was not associated with a higher risk of recurrent blood loss (adjusted HR 1.18, 95% CI 0.94 to 1.10) compared to the group that stopped warfarin. The group that restarted within seven days had a higher risk of GIB. However, the cumulative incidence of other groups was almost the same as that of the group that restarted after 30 days.

Thromboembolic event

The outcome measure thromboembolic event was reported in three studies (Witt, 2012; Sengupta, 2015; Qureshi, 2014).

Witt (2012) reported thrombosis in the first 90 days of follow-up. A total of 11 patients (2.5%) had a thrombotic event (six arterial (five strokes and one systemic embolism) and five venous (three pulmonary embolism and two DVT)). Three of the strokes were fatal. Of the 260 patients who restarted warfarin, one (0.4%) had a thrombotic event (DVT) compared to 10 of 182 patients (5.5%) who did not restart. Restarting warfarin after GIB was associated with a lower risk of thrombosis (HR: 0.05, 95% CI: 0.01 to 0.58) in a multivariate analysis using propensity scoring for CDS, age, and sex. The occurrence of thrombosis in patients who restarted warfarin did not depend on the duration of warfarin interruption.

In the study of Sengupta (2015), seven (4%) patients developed a thromboembolic event during the 90-day follow-up period. Overall, one of the 121 (0.8%) patients in group that restarted had a thrombotic event, compared with six of 76 (8%) patients in the group that did not resume anticoagulants. In multivariate analysis, restarting anticoagulants at hospital discharge was associated with a lower risk of thromboembolic events (HR 0.121, 95%CI 0.006 to 0.812).

In the study of Qureshi (2014), 221 (16.6%) patients developed a thromboembolic episode within one year of warfarin interruption. The risk was lower for patients who restarted warfarin (HR 0.71, 95%CI 0.54 to 0.93).

Level of evidence of the literature

The level of evidence for the outcome measures mortality, recurrent bleeding and thrombotic events has been downgraded to very low. The level of evidence started at low because these are non-randomized (retrospective) studies. In addition, due to limitations in the study design (difference in patient characteristics for which insufficient correction could be made), the level of evidence was further downgraded to very low.

Conclusions

Very low GRADE	The evidence is very uncertain about the effect of restarting anticoagulation therapy on mortality when compared with no restarting anticoagulation therapy in patients with an anticoagulation associated gastro-intestinal bleeding. *Sources (Witt, 2012; Sengupta, 2015; Qureshi, 2014)*

Very low GRADE	The evidence is very uncertain about the effect of restarting anticoagulation therapy on rebleeding when compared with no restarting anticoagulation therapy in patients with an anticoagulation associated gastro-intestinal bleeding. *Sources (Witt, 2012; Sengupta, 2015; Qureshi, 2014)*

Very low GRADE	The evidence is very uncertain about the effect of restarting anticoagulation therapy on thromboembolic events when compared with no restarting anticoagulation therapy in patients with an anticoagulation associated gastro-intestinal bleeding.

	Sources (Witt, 2012; Sengupta, 2015; Qureshi, 2014)

Part II: Intracranial bleeding

Summary of literature

Description of studies

Three (non-randomized) comparative studies including patients with intracranial hemorrhages were analyzed (Majeed, 2010; Gathier, 2013; Yung, 2012).

The study of Majeed (2010) described a multicenter cohort (three centers). Patients with warfarin-associated intracranial hemorrhage (radiologically confirmed) who had an INR of >1.5 at the time of hemorrhage were included. The occurrence of recurrent bleeding, thromboembolic complications and mortality in patients who were still alive after one week were analyzed. The analysis focused on patients at moderate to high risk of cerebral infarction (including patients with atrial fibrillation, mechanical heart valves, left ventricular thrombus, or previous cerebral infarction). A total of 234 patients met the inclusion criteria. For the 177 patients who survived the first week, the median follow-up duration was 69 weeks. Of these patients, 59 (33%) restarted warfarin. The patients who restarted warfarin were younger and had a longer follow-up than the patients who did not.

Yung (2012) reported on a cohort study that included follow-up patients with warfarin-related intracerebral hemorrhage (ICH, intracerebral or subarachnoidal) in one of 13 stroke centers in Canada (n=284). The main indications for anticoagulants were atrial fibrillation (67.3%), valve protheses (13.0%) and VTE (10.9%). Patients who restarted warfarin (n=91 (32%)) were compared with patients who did not restart warfarin (n=193 (68%)). Patients on antiplatelet therapy restarted warfarin less frequently. Patients with a cerebral infarction (in terms of neurological deficit) or with mechanical heart valve prostheses restarted more often. It is not clear whether the indications for the groups were different. Both crude data and the results of a logistic regression analysis are presented. In the multivariate analysis, the following variables were analyzed: age, sex, warfarin restart, Canadian Neurological Scale (CNS), presence of intraventricular blood, systolic blood pressure, diabetes, prior stroke or TIA, INR >3.0, and antiplatelet use.

In the study of Gathier (2013) patients with an ICH during treatment with acenocoumarol or phenprocoumon with an INR of at least 1.1 were included (N=38). Of these, 12 (32%) patients started antiplatelet therapy (TAR) and 15 (39%) patients started oral anticoagulation within two months of the ICH. Of the 15 patients who started oral coagulation, ten (67%) patients stopped oral anticoagulation again later. Reasons for discontinuation were that the treating physician no longer considered VKA to be indicated (n=4), recurrence of ICH (n=1), subdural hematoma (n=1), cerebral infarction with secondary hemorrhage (n=1), recurrent hematuria (n=1), patient's own choice (n=1), unknown (n=1) (Gathier, 2013).

One study reported the outcome measure of mortality (Yung, 2012). Two studies reported the outcome measure recurrent bleeding (ICH) (Majeed, 2010; Yung, 2012). Thrombotic events were reported in all three included studies (Majeed, 2010; Yung, 2012; Gathier, 2013). The results could not be pooled due to differences in study design and differences in the factors adjusted for in the multivariate analyses.

Results

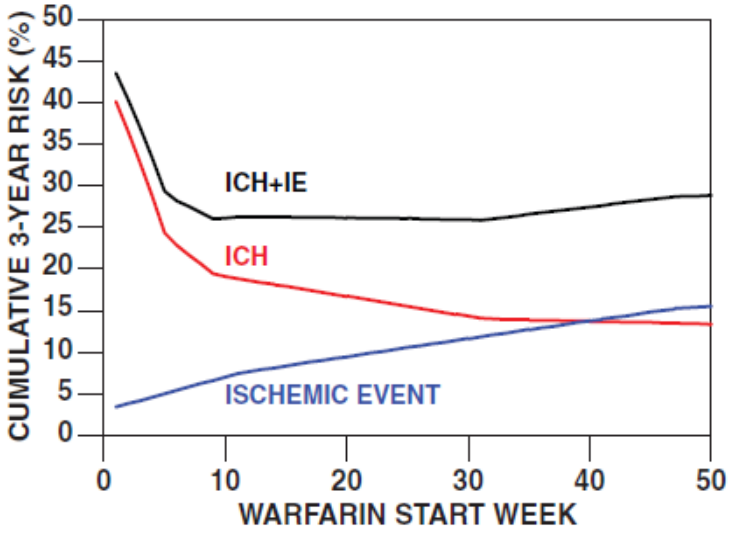
Mortality

In the study of Yung (2012) unadjusted mortality was higher for patients who did not restart warfarin compared to patients who did restart (50.8% versus 30.8%). After multivariable analysis adjusting for age, sex, stroke severity, initial INR, and comorbidities, restarting warfarin was not associated with a higher risk of death within 30 days (adjusted odds ratio (aOR) 0.49, 95%CI 0.26 to 0.93) or one year (aOR 0.79, 95%CI 0.43 to 1.43).

Recurrent bleeding

In the study of Majeed (2010) rates for intracranial hemorrhage or ischemic events (IE) were estimated using a Cox model. The model is based on patients with a cardiac indication for anticoagulants and/or with prior ischemic stroke who survived the first week without recurrence. Restarting warfarin increased the risk of recurrent intracranial hemorrhages (HR 5.57, 95%CI 1.80 to 17.25). The risk is calculated per patient-day. The daily risk of intracranial hemorrhage was lower for those who did not restart than for those who did restart (days one to 35: 0.18% vs. 0.75%; days 36 to 63: 0.044% vs. 0.20%; day 64 to 217: 0.0% vs. 0.20%; >218 days: 0.0% vs. 0.0069%) and decreased with time. The risk of ischemic events was higher for patients who did not restart compared to patients who restarted (day one to 77: 0.068% vs. 0.0%; day 78 to 329: 0.039% vs. 0.0%; >330 days: 0.017% vs. 0.0035%). These numbers were used to compile a figure comparing the cumulative risk of intracranial haemorrhages and ischemic events (IE) (see Figure 1).

Figure 1. The "total" risk for a treatment horizon of 3-years of recurrent intracranial hemorrhage (ICH)" and of ischemic events (IE) according to the time point of resumption of anticoagulation



In the study of Yung (2012), ICH-expansion or recurrence was not more common in the group that restarted warfarin than in the group that did not restart (unadjusted: 14 of 91 (15.4%) vs. 29 of 193 (15.0%)).

Thromboembolic event

The results for the outcome measure thromboembolic event in the study of Majeed (2010) are summarized in Figure 1 and the accompanying text (see above, i.e. ischemic events). Restarting warfarin reduced the risk of a thromboembolic event (HR 0.11, 95%CI 0.14 to 0.87)).

In the study of Yung (2012) it is reported that no thrombosis occurred within one year in the group of patients who restarted warfarin, and a nominally statistically insignificant number in the group of patients who did not restart. No exact numbers are mentioned.

In the study of Gathier (2013) outcomes per patient year (based on a total of 38 patients) were calculated. The primary outcome measure of stroke occurred twice in the control group in 35.4 patient years, compared to seven per 63.8 patient years with TARs and three per 19.5 patient years with oral anticoagulants. The incidence ratio of TARs versus control group was 2.7 (95%CI 0.5 to 16.3), OAC versus control group 1.9 (0.4 to 9.4).

Level of evidence of the literature

The level of evidence for the outcome measures thromboembolic event, bleeding and mortality was based on observational studies and therefore starts low. Because of additional limitations in the study design (difference in patient characteristics for which insufficient adjustments could be performed) the level of evidence was downgraded by one level to very low.

The included studies did not provide sufficient information concerning subgroups based on indications (AF versus mechanical heart valve) and contraindications (hypertensive intracerebral hemorrhage versus hemorrhage due to probable amyloid angiopathy).

Conclusions

Very low GRADE	The evidence is very uncertain about the effect of restarting anticoagulation therapy on mortality when compared with no restarting anticoagulation therapy in patients with an anticoagulation associated intracranial bleeding. *Source: Yung, 2012*

Very low GRADE	The evidence is very uncertain about the effect of restarting anticoagulation therapy on rebleeding when compared with no restarting anticoagulation therapy in patients with an anticoagulation associated intracranial bleeding. *Source: Majeed, 2010; Yung, 2012*

Very low GRADE	The evidence is very uncertain about the effect of restarting anticoagulation therapy on thromboembolic events when compared with no restarting anticoagulation therapy in patients with an anticoagulation associated intracranial bleeding. *Source: Majeed, 2010; Yung, 2012; Gathier, 2013*

Part III: Traumatic brain injury (TBI)

Summary of literature

Description of studies

In Albrecht (2014), bleeding and thrombotic events after discharge from the hospital after admission for TBI ("traumatic brain injury") were investigated based on insurance data (Medicare). Patients over the age of 64, who were admitted for TBI taking warfarin (or other anticoagulants, in the period before the TBI) were included. Patients who restarted warfarin after discharge (n=5811) were compared with patients who did not restart (n=4971). Many patients had atrial fibrillation (n= 8843 (82%)). The two groups were not comparable, with

patients who did not restart staying longer in hospital, more often transferred to a specialized nursing ward (n (%): C:4282 (40%), I: 1924 (33%)), more often having a CHADS2 score >2 (n (%) C:4223 (85%) vs. I:4774 (82%), and more often having a modified HEMORR2HAGES score >3 (N (%): C:2994 (60%) vs. I:3234 (56%)). The analysis compared two "early restart" groups (<3 months after discharge and resumption of anticoagulants <6 months after discharge) with two "late restart" groups (>3 and >6 months after discharge, resume). Interactions between the time of restart, risk of stroke (CHADS2 >2), bleeding risk (modified HEMORR2HAGES >3) were also investigated.

Results

Mortality

The outcome mortality is not reported in Albrecht (2014).

Recurrent bleeding

The risk of cerebral hemorrhages was higher in patients restarting warfarin, compared to patients who did not restart (risk ratio (RR) 1.51, 95%CI 1.29 to 1.78).

Thrombotic event

In the modified regression models, restarting warfarin reduced the risk of thrombotic events over a given period of time (RR 0.77, 95%CI 0.67 to 0.88). The combined hemorrhagic or ischemic stroke outcome was lower in patients restarting warfarin (RR 0.83, 95%CI 0.72 to 0.96). There was no difference between early restart and low restart of warfarin.

Level of evidence of the literature

The level of evidence for the outcome measures thromboembolic events and bleeding was based on observational studies and therefore started at low. Because of additional limitations in the study design (difference in patient characteristics for which insufficient correction can be made) the level of evidence have been downgraded by one level to very low. In addition, the study included patients with atrial fibrillation in particular. It is unclear to what extent the results can be extrapolated to other patient populations.

Conclusions

No GRADE	No evidence was found regarding the effect of restarting anticoagulation therapy on mortality when compared with no restarting anticoagulation therapy in patients using anticoagulation therapy with traumatic brain injury.

Very low GRADE	The evidence is very uncertain about the effect of restarting anticoagulation therapy on rebleeding when compared with no restarting anticoagulation therapy in patients using anticoagulation therapy with traumatic brain injury. *Source (Albrecht, 2014)*

Very low GRADE	The evidence is very uncertain about the effect of restarting anticoagulation therapy on thromboembolic events when compared with no restarting anticoagulation therapy in patients using anticoagulation therapy with traumatic brain injury. *Source (Albrecht, 2014)*

Updated search 2023

As already described, no RCT could be included from the updated search. Seven cohort studies fulfilled selection criteria. However, the working group is of the opinion that these observational data will be insufficient to provide a clear answer, i.e. the levels of evidence will still remain very low. It was therefore decided not to update the previous literature analysis but to provide a concise overview of the additional observation cohorts (N=7). General characteristics and the main findings are reported in Table 1. All studies reported on recurrent bleedings and thrombotic events. Sengupta (2018) and Tapaskar (2022) did not report on mortality and only included events resulting in hospital readmissions.

Part I: Gastro-intestinal bleeding

Two studies included patients with anticoagulation-associated gastro-intestinal bleedings (Tapaskar, 2022; Sengupta, 2018). One study (Little, 2021) included a mixed population (i.e. gastro-intestinal, intracranial and other), but reported data on the subgroups separately.

Mortality

In the cohort of Little (2021) a lower mortality risk was found for patients restarting anticoagulation, compared to no restarting (HR (95%CI): 0.54 (0.47 to 0.56). This effect estimate is in line with the findings of the initial literature analysis. Sengupta (2018) and Tapaskar (2022) did not report on mortality.

Rebleeding

In all three cohorts increased risks were observed for rebleedings for patients restarting anticoagulation, which is in line with the initial literature analysis. HRs ranged from 1.43 to 2.21. Tapaskar (2022) investigated warfarin and DOACs separately and observed a somewhat smaller effect estimate for restarting DOACs (HR: 1.43). This is consistent with the findings of Sengupta (2018). See Table 1 for further details.

Thromboembolic event

In the study of Tapaskar (2022) restart of both warfarin as well as DOACs was associated with a lower risk for thromboembolic events (hospital admissions), compared to no restart. This agrees to the findings of Little (2021). HRs ranged from 0.52 to 0.61. These findings agrees with the initial literature analysis. In the study of Sengupta (2018) however no association was found.

Part II: Intracranial bleeding

Four studies included patients with anticoagulation-associated intracranial bleedings (Biffi, 2017; Lin, 2022; Nielsen, 2017; Newman, 2020). One study (Little, 2021) included a mixed population (i.e. gastro-intestinal, intracranial and other), but reported data on the subgroups separately.

Mortality

In all four studies lower mortality risks were found for patients restarting anticoagulation. The effect estimates ranges from 0.27 to 0.85. See Table 1 for details.

Rebleeding

Four of the five studies observed an increased risk for rebleedings in case of restart of anticoagulation, with effect estimates ranging from 1.20 to 2.20. In contrast, in the study of Newman (2020) a lower risk was observed (HR (95%CI): 0.62 (0.41 to 0.95). See Table 1 for further details.

Thromboembolic event

The studies observed lower risks for thrombosis in patients restarting anticoagulation. The effect estimates in the five additional cohorts range from 0.44 to 0.85. See Table 1 for further details.

Conclusion

The cohort studies found in the updated literature search, consistently showed higher risk for rebleedings and lower risks for thrombosis and mortality in patients restarting anticoagulation. These findings are broadly in line with the initial analysis of the literature. The more recent studies are larger and generally use more sophisticated methods to adjust for differences in patient characteristics between patients restarting and not restarting anticoagulation after an anticoagulation-associated bleeding. However, confounding by indication can still be present. In addition, the studies vary in several general characteristics such as type of anticoagulation, timing of restart and baseline.

	Country	Population	Comparison	Timing of resumption of anticoagulation	Baseline	Follow-up	Outcomes (critical) Mortality/major bleeding/TE (Resuming versus not)	Remarks
Intracranial bleeding								
Newman, 2020	USA	AF patients with ICH N=1,502	NOAC vs Warfarin vs Control	<= 6 weeks	6 wks after index event	Mean of 780 days	OAC/no OAC Mortality: HR 0.48 (95%CI 0.37–0.62) TE: HR 0.85 (95%CI 0.55–1.32) Recurrent ICH: HR 0.62 (95%CI 0.41–0.95)	Time-dependent analysis
Nielsen, 2017	Denmark	Patients with AF and ICH N=2415 (N=1325 with hemorrhagic stroke and 1090 with traumatic ICH)	Warfarin vs no warfarin	Not reported	14 days after discharge	Median of 279 days	Population hemorrhagic stroke: Recurrent ICH: aHR 1.31 (95%CI: 0.68-2.50) IS/SE: aHR 0.49 (95%CI 0.24-1.02) All-cause mortality: aHR 0.51 (95%CI 0.37-0.71)	Propensity-matched analysis (sensitivity analysis), Time-dependent analysis
Lin, 2022	Taiwan	AF patients with ICH	OAC (N=283) vs no AT (N=1069) OAC (N=283) vs antiplatelet (N=214)	Median of 42 days from discharge	90 days after hospital discharge	Median of 0.7 yrs	OAC vs no AT: All-cause mortality: HR 0.85 (95%CI 0.72–1.01) Major bleeding: HR 1.40 (95%CI 0.99–1.98) TE: HR 0.60 (95%CI 0.43–0.84)	IPTW-analysis
Biffi, 2017	Germany and USA	AF patients with ICH (non-trauma) N=1,012	OAT (warfarin) vs no OAT	Within 90 days of index ICH	Date of ICH	1 year	Mortality: HR 0.27 (95%CI 0.19–0.40) Recurrent ICH: HR 1.20 (95%CI 0.95–1.58)	Propensity score matching, time-varying analysis

	Country	Population	Comparison	Timing of resumption of anticoagulation	Baseline	Follow-up	Outcomes (critical) Mortality/major bleeding/TE (Resuming versus not)	Remarks
	(joint analysis of 3 studies)						Ischemic stroke: HR 0.44 (95%CI 0.29–0.66)	
Gastro-intestinal bleeding								
Tapaskar 2022	USA	AF patients on warfarin or DOACs and hospitalized for GIB (within 1 year of start OAC) (discharged) 2008-2017 N=2991	Resumptions vs no resumption of OAC Separately for warfarin and DOAC	Within 90 days of discharge	Date of discharge	180 days	<u>Recurrent GIB (hospital admissions)</u> Warfarin: HR 2.12 (95%CI 1.43–3.14) DOAC: HR 1.43 (95%CI 0.81-2.52) <u>TE (hospital admissions)</u> Warfarin: HR 0.61 (95%CI 0.39–0.96) DOAC: HR 0.52 (95%CI 0.28–0.98)	Time-dependent analysis Secondary analysis: propensity-score matching. Only hospital admissions
Sengupta, 2018	USA	2010-2014 N=1338 Treated with DOAC and hospitalized for GIB within 1 year	DOAC within 30 days vs no DOAC within 30 days	Within 30 days of discharge	Date of discharge	6 months	Readmissions for TE: HR 0.99 (95%CI 0.53–1.70) Readmissions for GIB HR 1.56 (95%CI 0.95–2.47)	Only hospital admissions included
Other/combined bleeding								
Little, 2021	Canada	Older patients (>65 years), hospitalized for bleeding while receiving OAC's	Resumtion vs no resumption of OAC's within 1 year	Median time: 46 days	100 days after hospital discharge	Median of 82 weeks(restart) and 83 weeks (no restart)	<u>GIB</u> Bleeding: HR 2.02 (95%CI 1.69-2.40) Thrombosis: HR 0.56 (95%CI 0.44-0.71)	Time-varying analysis

	Country	Population	Comparison	Timing of resumption of anticoagulation	Baseline	Follow-up	Outcomes (critical) Mortality/major bleeding/TE (Resuming versus not)	Remarks
		N=6793 GIB: N=4297 ICH: N=805 Other: N=1691					All-cause mortality: HR 0.54 (95%CI 0.47-0.56) <u>Intracranial</u> Bleeding: HR 2.20 (95%CI 1.36-3.56) Thrombosis: HR 0.73 (95%CI 0.44-1.23) All-cause mortality: HR 0.54 (95%CI 0.43-0.68) <u>Other</u> Bleeding: HR 1.50 (95%CI 1.15-1.98) Thrombosis: HR 0.60 (95%CI 0.41-0.89) All-cause mortality: HR 0.54 (95%CI 0.43-0.68)	

AF: atrial fibrillation, aHR: adjusted hazard ratio, DOAC: direct oral anticoagulants, GIB: gastrointestinal bleeding, HR: hazard ratio, ICH: intracerebral haemorrhage, OAC: oral anticoagulants, TE: thrombo-embolic event.

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Op basis van de geïncludeerde studies is het effect onzeker van het herstarten van de antistollingsbehandeling bij patiënten die een gastro-intestinale of intracraniële bloeding hadden tijdens het gebruik van antistollingsmiddelen, op de cruciale uitkomsten mortaliteit en recidief bloeding. Dit geldt ook voor de patiënten die een traumatisch hoofdletsel opliepen tijdens het gebruik van antistollingsmiddelen. Voor deze groep patiënten waren er geen data beschikbaar met betrekking tot de cruciale uitkomstmaat mortaliteit.
Ook voor de belangrijke uitkomstmaat trombo-embolische events geldt dat er grote onzekerheid bestaat over het effect van het herstarten van antistollingsbehandeling bij patiënten die een gastro-intestinale bloeding, intracraniële bloeding of traumatisch hoofdletsel hadden tijdens het gebruik van antistollingsmiddelen. De overall bewijskracht voor deze module is dan ook zeer laag en er is duidelijk sprake van een kennisvraag.

Er is geen bewijs uit gerandomiseerde fase-3 klinische trials met betrekking tot de vraag of en wanneer orale antistollingsmiddelen hervat dienen te worden bij patiënten die een gastro-intestinale bloeding, intracraniële bloeding, of traumatisch hersenletsel hebben doorgemaakt en een blijvende indicatie voor deze medicatie hebben. In een fase-2 gerandomiseerde studie werden patiënten met atriumfibrilleren die een antistolling gerelateerde hersenbloeding door hadden gemaakt (N=101) gerandomiseerd voor herstart van de antistolling (apixaban) of vermijden van antistolling (plaatjesremming of geen antitrombotica) (Schreuder, 2021). In totaal werd er voor 13/50 (26%) patiënten in de groep die antistolling ontving, een niet-fatale beroerte of cardiovasculaire dood gerapporteerd, ten opzichte van 12/51 (24%) van de patiënten in de groep waarbij geen antistolling werd herstart. De conclusie is dat patiënten met een antistolling gerelateerde hersenbloeding een hoog risico hebben op een niet-fatale beroerte dan wel vasculaire dood, ongeacht het al dan niet starten van antistolling.
In een andere gerandomiseerde *non-inferiority* pilot studie werden patiënten met een hersenbloeding en AF en een CHA2DS2-VASc score ≥2 geïncludeerd (N=203; Salman, 2021). 16% van de patiënten gebruikte geen antistolling ten tijde van de hersenbloeding. In deze studie werd het effect van het starten van orale antistolling vergeleken met het effect van plaatjesremmers of geen antitrombotica. In totaal kregen 8/101 (8%) patiënten in de groep waarbij de antistolling gestart werd opnieuw een intracraniële bloeding ten opzichte van 4/102 (4%) van de patiënten in de groep waarbij er geen orale antistolling werd gestart. In de groep waarbij orale antistolling werd gestart overleden 22/101 (22%) van de patiënten, ten opzichte van 11 (11%) in de controlegroep. De auteurs concluderen dat het onzeker is of het starten van orale antistolling niet-inferieur is aan het niet starten van orale antistolling na een doorgemaakte hersenbloeding.

Het kantelpunt van voor- en nadelen is op basis van de beschikbare literatuur niet aan te wijzen. De belangrijkste vraag die uit de cohortstudies naar voren komt is of herstart van antistolling inderdaad de mortaliteit verlaagt, of dat dit een artefact is dat voortkomt uit selectie (*confounding by (contra-) indication*) van patiënten in de observationele studies. Hierop kan nu geen antwoord worden gegeven.

Gastro-intestinale bloeding

Patiënten met een ernstige gastro-intestinale bloeding hebben een aanzienlijk risico op trombose als niet met antistolling wordt herstart, bijvoorbeeld patiënten die antistollingsmiddelen gebruiken in verband met een mitraliskunstklep. Voor deze uitkomstmaat geldt dat, als er selectiebias is, dan het aantal patiënten met een trombose zou zijn onderschat. Het risico op bloedingen lijkt vooral groot als er snel (binnen een week, voor ontslag) wordt herstart met antistolling en de oorzaak van de bloeding niet adequaat

kon worden gevonden en aangepakt. Het lijkt in deze situatie dus reëel om, als er een aanhoudende indicatie is voor antistolling, wel te herstarten maar daarmee wat langer te wachten. Er is geen onderbouwing voor welke termijn moet worden gekozen, maar in de praktijk lijkt twee weken redelijk. Hierbij dient rekening gehouden te worden met de ernst, locatie en behandeling van de bloeding, alsook met de hoogte van het trombotisch risico. In het geval dat de oorzaak van de bloeding wel kon worden opgespoord en aangepakt, zoals bijvoorbeeld bij een bloedend ulcus duodeni, kan bij voldoende hemostase eerder worden herstart met antistollingsmedicatie.

Intracraniële bloeding
In de richtlijn van de European Heart Rhythm Association uit 2021 wordt geen harde aanbeveling gedaan over het wel of niet herstarten van antistolling na een intracraniële bloeding, noch over de eventuele timing hiervan (Steffel, 2021). Per patiënt dient een individuele afweging gemaakt te worden, bij voorkeur in multidisciplinair verband. Factoren die meegewogen kunnen worden bij de beslissing tot herstarten zijn onder andere of er een behandelbare oorzaak van de bloeding is, de aanwezigheid van cerebrale microbloedingen, de ernst van de intracraniële bloeding, de leeftijd van de patiënt, alcohol misbruik en de aanwezigheid van ongecontroleerde hypertensie. Indien besloten wordt tot herstart van antistolling, dan kan een periode van 4-8 weken na het optreden van de bloeding worden aangehouden (Steffel, 2021).

Majeed (2010) concluderen dat herstarten na 10 tot 30 weken vanaf de intracraniële bloeding optimaal lijkt op basis van het gecombineerde cumulatieve risico op bloedingen of ischemische events voor een behandelhorizon van drie jaar. Dit is veel later dan in Nederland gebruikelijk is.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>
Bij de beslissing tot wel of niet herstarten van de antistollingsbehandeling is het van belang om de wens van de patiënt mee te nemen. Bespreek met patiënt het gebrek aan wetenschappelijk bewijs en de potentiële voor- en nadelen van de verschillende strategieën. Het belangrijkste potentiële voordeel van het herstarten van de antistolling is het voorkomen van trombo-embolische complicaties. Het belangrijkste potentiële nadeel is het opnieuw optreden van een bloedingscomplicatie.

<u>Kosten (middelenbeslag)</u>
Kosten spelen geen rol in de afweging om antistolling al dan niet te herstarten bij patiënten die antistolling gebruikten en een bloeding kregen.

<u>Aanvaardbaarheid, haalbaarheid en implementatie</u>
Overwegingen omtrent aanvaarbaarheid, haalbaarheid en implementatie spelen geen rol bij de huidige aanbeveling.

Aanbeveling
<u>Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies</u>
Het belangrijkste voordeel van het herstarten van antistolling is een afname van het risico op een trombo-embolisch event. Het belangrijkste nadeel is een verhoging van het risico op een nieuwe bloeding. Omdat data uit gerandomiseerde studies met een adequate sample size ontbreken, is er een zwakke aanbeveling geformuleerd.

Maak voor elke patiënt die een intracraniële of ernstige gastro-intestinale bloeding heeft doorgemaakt een afweging tussen enerzijds het risico op een arteriële of veneuze trombose en anderzijds het risico op een nieuwe bloeding bij het hervatten van de antistollingsbehandeling. Deze beslissing wordt bij voorkeur in een multidisciplinair overleg genomen en in samenspraak met de patiënt en de behandelend specialist. Houd hierbij rekening met de ernst, de locatie en de behandeling van de bloeding alsook met de hoogte van het trombotisch risico.

Overweeg de antistollingstherapie niet te snel te hervatten:

- twee weken na een ernstige gastro-intestinale bloeding;
- één tot tien weken na een intracraniële bloeding.

Kennisvragen

Wat zijn de effecten van het (vroeg) herstarten van antistolling bij patiënten die een antistolling gerelateerde bloeding kregen, vergeleken bij niet of laat herstarten van de antistollingsbehandeling?

Literatuur

Albrecht JS, Liu X, Baumgarten M, et al. Benefits and risks of anticoagulation resumption following traumatic brain injury. JAMA Intern Med. 2014;174(8):1244-51.

Biffi A, Kuramatsu JB, Leasure A, Kamel H, Kourkoulis C, Schwab K, Ayres AM, Elm J, Gurol ME, Greenberg SM, Viswanathan A, Anderson CD, Schwab S, Rosand J, Testai FD, Woo D, Huttner HB, Sheth KN. Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage. Ann Neurol. 2017 Nov;82(5):755-765. doi: 10.1002/ana.25079. Epub 2017 Oct 31. PMID: 29028130; PMCID: PMC5730065.

Little DHW, Sutradhar R, Cerasuolo JO, Perez R, Douketis J, Holbrook A, Paterson JM, Gomes T, Siegal DM. Rates of rebleeding, thrombosis and mortality associated with resumption of anticoagulant therapy after anticoagulant-related bleeding. CMAJ. 2021 Mar 1;193(9):E304-E309. doi: 10.1503/cmaj.201433. PMID: 33649169; PMCID: PMC8034308.

Gathier CS, Algra A, Rinkel GJ, et al. Long-term outcome after anticoagulation-associated intracerebral haemorrhage with or without restarting antithrombotic therapy. Cerebrovasc Dis. 2013;36(1):33-7.

Lin SY, Chang YC, Lin FJ, Tang SC, Dong YH, Wang CC. Post-Intracranial Hemorrhage Antithrombotic Therapy in Patients With Atrial Fibrillation. J Am Heart Assoc. 2022 Mar 15;11(6):e022849. doi: 10.1161/JAHA.121.022849. Epub 2022 Mar 4. PMID: 35243876; PMCID: PMC9075312.

Majeed A, Kim YK, Roberts RS, et al. Optimal timing of resumption of warfarin after intracranial hemorrhage. Stroke. 2010;41(12):2860-6.BACKGROUND AND PURPOSE: The optimum timing of resumption of anticoagulation after warfarin-related intracranial hemorrhage in patients with indication for continued anticoagulation is uncertain. We performed a large retrospective cohort study to obtain more precise risk estimates.

Newman TV, Chen N, He M, Saba S, Hernandez I. Effectiveness and Safety of Restarting Oral Anticoagulation in Patients with Atrial Fibrillation after an Intracranial Hemorrhage: Analysis of Medicare Part D Claims Data from 2010-2016. Am J Cardiovasc Drugs. 2020 Oct;20(5):471-479. doi: 10.1007/s40256-019-00388-8. PMID: 31808136; PMCID: PMC7274872.

Nielsen PB, Larsen TB, Skjøth F, Lip GY. Outcomes Associated With Resuming Warfarin Treatment After Hemorrhagic Stroke or Traumatic Intracranial Hemorrhage in

Patients With Atrial Fibrillation. JAMA Intern Med. 2017 Apr 1;177(4):563-570. doi: 10.1001/jamainternmed.2016.9369. PMID: 28241151; PMCID: PMC5470390.

Qureshi W, Mittal C, Patsias I, et al. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. Am J Cardiol. 2014;113(4):662-8.

SoSTART Collaboration. Effects of oral anticoagulation for atrial fibrillation after spontaneous intracranial haemorrhage in the UK: a randomised, open-label, assessor-masked, pilot-phase, non-inferiority trial. Lancet Neurol. 2021 Oct;20(10):842-853. doi: 10.1016/S1474-4422(21)00264-7. Epub 2021 Sep 3. PMID: 34487722.

Schreuder FHBM, van Nieuwenhuizen KM, Hofmeijer J, Vermeer SE, Kerkhoff H, Zock E, Luijckx GJ, Messchendorp GP, van Tuijl J, Bienfait HP, Booij SJ, van den Wijngaard IR, Remmers MJM, Schreuder AHCML, Dippel DW, Staals J, Brouwers PJAM, Wermer MJH, Coutinho JM, Kwa VIH, van Gelder IC, Schutgens REG, Zweedijk B, Algra A, van Dalen JW, Jaap Kappelle L, Rinkel GJE, van der Worp HB, Klijn CJM; APACHE-AF Trial Investigators. Apixaban versus no anticoagulation after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation in the Netherlands (APACHE-AF): a randomised, open-label, phase 2 trial. Lancet Neurol. 2021 Nov;20(11):907-916. doi: 10.1016/S1474-4422(21)00298-2. PMID: 34687635.Sengupta N, Feuerstein JD, Patwardhan VR, et al. The risks of thromboembolism vs. Recurrent gastrointestinal bleeding after interruption of systemic anticoagulation in hospitalized in patients with gastrointestinal bleeding: a prospective study. Am J Gastroenterol. 2015;110(2):328-35.

Sengupta N, Marshall AL, Jones BA, Ham S, Tapper EB. Rebleeding vs Thromboembolism After Hospitalization for Gastrointestinal Bleeding in Patients on Direct Oral Anticoagulants. Clin Gastroenterol Hepatol. 2018 Dec;16(12):1893-1900.e2. doi: 10.1016/j.cgh.2018.05.005. Epub 2018 Jun 30. PMID: 29775794.

Tapaskar N, Ham SA, Micic D, Sengupta N. Restarting Warfarin vs Direct Oral Anticoagulants After Major Gastrointestinal Bleeding and Associated Outcomes in Atrial Fibrillation: A Cohort Study. Clin Gastroenterol Hepatol. 2022 Feb;20(2):381-389.e9. doi: 10.1016/j.cgh.2020.11.029. Epub 2020 Nov 21. PMID: 33227428.

Witt DM, Delate T, Garcia DA, et al. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. Arch Intern Med. 2012;172(19):1484-91.

Yung D, Kapral MK, Asllani E, et al. Reinitiation of anticoagulation after warfarin-associated intracranial hemorrhage and mortality risk: the Best Practice for Reinitiating Anticoagulation Therapy After Intracranial Bleeding (BRAIN) study. Can J Cardiol. 2012;28(1):33-9.

Bijlagen bij module herstarten antistollingstherapie na een bloeding

Implementatieplan

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijke kennisvraag
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	Sterkte van de aanbeveling	Bewijskracht per uitkomstmaat	Verkeerslicht per (sub)aanbeveling
Maak voor elke patiënt die een intracraniële of ernstige gastro-intestinale bloeding heeft doorgemaakt een afweging tussen enerzijds het risico op een arteriële of veneuze trombose en anderzijds het risico op een nieuwe bloeding bij het hervatten van de antistollingsbehandeling. Deze beslissing wordt bij voorkeur in een multidisciplinair overleg genomen en in samenspraak met de patiënt en de behandelend specialist. Houd hierbij rekening met de ernst, de locatie en de behandeling van de bloeding alsook met de hoogte van het trombotisch risico. Overweeg de antistollingstherapie niet te snel te hervatten: • twee weken na een ernstige gastro-intestinale bloeding; • één tot tien weken na een intracraniële bloeding.	□ Sterk (doe/ gebruik) / **X** Zwak (overweeg)	Overall bewijskracht □ **H** □ **M** □ **L X VL** □ **NG** **Range bewijskracht van alle uitkomstmaten** □ **H** □ **M** □ **L X VL** **X NG** **OF** □ **voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	□ **ROOD:** vul tabel A in □ **LICHT ROOD:** vul tabel A in **X ORANJE:** gebruik tabel B □ **LICHT GROEN:** vul tabel A in □ **GROEN:** vul tabel A in

5 Implementatietabel

Aanbeveling Maak voor elke patiënt die een intracraniële of ernstige gastro-intestinale bloeding heeft doorgemaakt een afweging tussen enerzijds het risico op een arteriële of veneuze trombose en	Op basis van de beschikbare evidentie en ervaring uit de praktijk kon er onvoldoende richting aan de besluitvorming worden gegeven. Om die reden is er geen beschrijving van belemmeringen en kansen voor implementatie van de aanbeveling toegevoegd. Disseminatie van de kennis in deze module verloopt via de standaard route. De module wordt gepubliceerd op de Richtlijnendatabase.

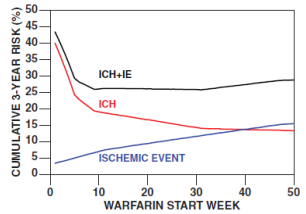
anderzijds het risico op een nieuwe bloeding bij het hervatten van de antistollingsbehandeling. Deze beslissing wordt bij voorkeur in een multidisciplinair overleg genomen en in samenspraak met de patiënt en de behandelend specialist. Houd hierbij rekening met de ernst, de locatie en de behandeling van de bloeding alsook met de hoogte van het trombotisch risico. Overweeg de antistollingstherapie niet te snel te hervatten: • twee weken na een ernstige gastro-intestinale bloeding; • één tot tien weken na een intracraniële bloeding.	

Evidence tables

Initial search

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series])

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
ICH							
Majeed, 2010	Type of study: Retrospective cohort Setting: Multicentre Country: Sweden, Canada Source of funding: S.S. received consulting fees from many pharma, H.M. has received lecure fees from pharma, others have	Inclusion criteria: Patients treated with warfarin, diagnosis (radiologically confirmed) of intracranial haemorrhage (ICD-10: 1600-1629), INR>1.5 Exclusion criteria: haemorrhage caused by severe accidents with multi-trauma or haemorrhagic transformation of ischemic stroke, death <1week after bleeding N total at baseline: 234 (first week survivors n=177) Important prognostic factors: *median ± IQR:* *total: 75 (65-80)* *I: 70 (63-77)* *C: 78 (70.5-72)** *Sex male, n (%):* *Total: 112 (63)* *I: 31 (69)* *C:56 (64)*	No resumption of warfarin	Resumption of warfarin (different time periods) (n=59, 33%)	Length of follow-up: Median 69 weeks (IQR 19-144) Loss-to-follow-up: 113 (48%) of the patients died during follow up, with median survival of 4.5 years. Incomplete outcome data: Intervention: N (%)	I vs. C Cox proportional hazards model at different time intervals without (I) and with (C) resumption of warfarin: Risk of recurrent intracranial haemorrhage per day 1-35 days: 0.18%vs. 0.75% HR: 4.13 36-63 days: 0.044% vs. 0.20% HR: 4.46 64-217 days: 0.0% vs. 0.20% HR: ∞ >218 days: 0.0% vs. 0.0069% HR: ∞	The modelling of risk for recurrent intracranial haemorrhage vs. ischemic stroke in patients with or without resumption of warfarin therapy is based on the population with cardiac indication for anticoagulation and/or with previous ischemic stroke and who had survived the first week without a recurrent event (n=132). Resumption of warfarin at any given time point will increase the subsequent risk of recurrent intracranial haemorrhage and reduce the risk of a thromboembolic event. The optimal restart time must balance these 2 competing cumulative risks over the entire warfarin "treatment horizon". To determine the optimal restart time, we varied warfarin resumption between 1 and 50 weeks after the index intracranial bleed and calculated the total risk (before +

	no potential conflicts of interest.	*Indication for anticoagulation* *Total; I; C, n(%)* *AF: 102 (58); 22 (49); 79 (91)* *VT: 30 (17); 0; 0* *Mechanical aortic valve:19 (11); 15 (33); 4 (5)* *Mechanical mitral valve:9 (5); 7 (16); 2(2)* *Other 17 (10); 1(2); 2(2):* Groups comparable at baseline? Patients who did not resume warfarin were significantly older.			Reasons (describe) Control: N (%) Reasons (describe)	<u>Risk of ischemic event per day</u> 1-77 days: 0.068%vs. 0.0% HR: 0.00 78-329 days: 0.039% vs. 0.0% HR: 0.0 >330 days: 0.017% vs. 0.0035% HR: 0.21	after selected time point of resumption) of recurrence IH and of thromboembolic event through to the end of treatment. The calculation of cumulative risks used the rated displayed left (outcome). Given that it is implausible that the actual risk of intracranial bleed or thromboembolic event is 0, we have not used the observed daily risks directly, but instead we have blended the observed rates and cox model hazard ratio.  **Figure 2.** The "total" risk for a treatment horizon of 3 years of recurrent intracranial hemorrhage and of ischemic stroke according to the time point of resumption of anticoagulation. The results (figure) demonstrate how the total risk of intracranial haemorrhage and an ischemic event for the whole treatment period varies according to when warfarin is restarted. Based on this combined risk the optimal period of resumption of warfarin seems to be between 10 and 30weeks from the index intracranial haemorrhage over a survival- and treatment-horizon of 3 years.

Yung, 2012	Type of study: Setting: Cohort Country: Canada Source of funding: none	Inclusion criteria: Warfarin related ICH (intracerebral or subarachnoid) submitted to 13 stroke centres, >18 years, who were or were not restarted on warfarin after hospitalization. Exclusion criteria: previous ICH of any type, other concurrent active bleeding process, pregnancy, bleeding diathesis precluding reinitiation of warfarin, recent trauma, hemorrhagic conversion from ischemic stroke, neurosurgical instrumentation, intracranial neoplasia, were palliative, or if thrombolysis was administered. N total at baseline: 284 Intervention: 91 Control: 193 Important prognostic factors[2]: age ± SD: I: 71.8 (12.9) C: 74.4 (11.9) P=0.11 Sex: I: 46 (50.5) C: 110 (57.0) P=0.31 Stroke type: Intracerebral hemorrhage I: 78 (85.7) C: 174 (90.2) Subarachnoid hemorrhage I: 13 (14.3) C: 19 (9.8)	Warfarin was restarted (n=91) in hospital	Warfarin not restarted (n=193)	Length of follow-up: 1 year Loss-to-follow-up: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe) Incomplete outcome data: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe)	**Unadjusted outcomes I vs. C**, n (%) Death: In hospital: 30 (33.0) vs. 98 (50.8) p=0.005 1 month: 29 (31.9) vs. 105 (54.4) p=0.001 6 months: 38 (41.8) vs. 114 (59.1) p=0.006 1 year: 44 (48) vs. 118 (61) P=0.04 ICH expansion or recurrrence (haemorrhage recurrence of expansion confirmed on serial CT or MRI): 14 (15.4) vs. 29 (15.0) P=0.94 Death or intracranial bleeding: 1 month: 32 (35.2) vs. 106 (54.9) p=0.002 1 year: 46 (50.5) vs. 118 (61.1) p=0.09 Death, bleeding, or thrombotic complication at 1 year: 47 (51.60) vs. 119 (61.7) p=0.11 **Multivariate analysis** Mortality (30 days):	Data was collected from the registry of the Canadian stroke network (includes audit information prospectively collected on all consecutive patients with acute stroke or TIA evaluated in the ER and admitted to hospital at acute institutions; combined with data from the registered persons database. Multivariate logistic regression model was performed including potential clinical variables with p<0.25 on univariate analysis. Variables examined in multivariable analysis for warfarin reinitiation included: age, gender, CNS score, mechanical valve prosthesis, hypertension, previous stroke or TIA, and antiplatelet use on admission. Variables considered in multivariable analysis of all-cause mortality and bleeding included: age, gender, warfarin reinitiation, CNS score, presenece of intraventricular haemorrhage, systolic BP, diabetes, previous stroke or TIA, INR >3.0 and antiplatelet use. In multivariable analysis, patients receiving concurrent antiplatelet therapy on admission were less likely to be restarted on warfarin

		P=0.27 GCS score: I: 10.2 (3.9) C: 7.2 (3.6) P=0.001 Atrial fibrillation at admission: I: 46 (50.5) C: 89 (46.1) P=0.49 Prosthetic valve: I: 19 (20.9) C: 18 (9.3) P=0.007 Antiplatelet use: I: 12 (13.2) C:45 (23.3) P=0.047 The main indications for anticoagulation included atrial fibrillation or flutter (67.3%), valve prosthesis (13.0%), and venous thromboembolic disease (10.9%). Groups comparable at baseline? No				aOR: 0.49 (0.26-0.93) p=0.03 mortality (1 year) aOR: 0.79 (0.43-1.43) p=0.43	(adjusted odds ratio [aOR], 0.34; 95% confidence interval [CI], 0.16-0.74; P 0.007). Warfarin was more likely to be restarted in those with less severe stroke (CNS score < 7; aOR, 2.07; 95% CI, 1.20-3.57; P 0.009) or with valve prostheses in situ (aOR 3.07; 95% CI, 1.29-7.27; P 0.011). Prior stroke or TIA, gastrointestinal bleeding, cirrhosis, renal disease, hypertension, CHADS2 score, presentation INR (———— 3.0), BP, stroke location, and age were not associated with warfarin reinitiation. Our findings suggest that patients with mild-to-moderate stroke severity (ie, CNS score <7) without intraventricular involvement and admission INR ———— 3.0 may be restarted on warfarin without an excess risk of hemorrhage expansion or death. Patients that are high thrombotic risk with indications for long-term warfarin may be considered for reinitiation in-hospital, although the exact timing of reinitiation warrants further evaluation. Conversely, patients at high risk for thrombosis with either severe stroke (CNS score >7), intraventricular hemorrhage, or supratherapeutic INR on presentation should be carefully evaluated on an individual

							basis as they are more prone to poor outcomes. The routine use of neuroimaging to rule out intracranial hematoma expansion prior to reinitiating therapy may be reasonable. Finally, all decisions should be made in the context of each patient's unique clinical circumstances and comorbidities. Patients who are not at high thrombotic risk may not derive net clinical benefit from early reinitiation of warfarin if the potential for in-hospital hematoma expansion or recurrent intracranial bleeding remains high.
Gathier, 2013	Type of study: retrospective follow-up study Setting: Hospital Country: Netherlands Source of funding: H.B. van der Worp has served as a consultant to Bristol-Meyers	Inclusion criteria: ICH while treated with acenocoumarol or phenprocoumom at time of ICH, INR ≥1.1, discharge from hospital Exclusion criteria:- N total at baseline: 40 I1 (OAC): 12 I2 (APM): 13 Control (No ATM): 13 Important prognostic factors[2]: *age ± SD:* I1 (OAC): 70 (54-86) I2 (APM): 74 (44-87) Control (No ATM): 69 (48-85) Reason for OAC Atrial fibrillation:	I1 (OAC): oral anticoagulation was restarted within 2 months after ICH I2 (APM): antiplatelet therapy was restarted within 2 months after ICH	No antithrombotic medication was started within 2 months after ICH	Length of follow-up: Median: 3.5 years Loss-to-follow-up: 2, 1 reason unknown, 1 declined responding to questionnaire Incomplete outcome data: Intervention:	**Any stroke** n I1 (OAC): 3 I2 (APM): 7 Control (No ATM): 2 Incidence per patient year: I1 (OAC): 15.4 I2 (APM): 11.0 Control (No ATM): 5.6 Incidence ratio (when compared to no ATM): (95%CI) I1 (OAC): 2.7 (0.5-16.3) I2 (APM): 1.9 (0.4-9.4) **Cerebral infarction**, n I1 (OAC): 2	Data were obtained by reviewing medical records and mailed questionnaires APM: antiplatelet therapy ATM: antitrombotic medication OAC: oral anticoagulation The total of patient-years (PY) on OAC, antiplatelet therapy, and no antithrombotic medication after the ICH was calculated until the occurrence of an event or – in case no event occurred – until the date the questionnaire was administered or the date of death, whichever came first.

	Squibb.	I1 (OAC): 4 (33) I2 (APM): 8 (62) Control (No ATM): 6 (46) Heart valve replacement: I1 (OAC): 2 (17%) I2 (APM): 0 Control (No ATM):0 Myocardial infarction I1 (OAC): 0 I2 (APM): 2 (15) Control (No ATM): 2 (15) DVT/PE: I1 (OAC): 4 (33) I2 (APM): 0 Control (No ATM): 2 (15) Cerebral infarction I1 (OAC): 0 I2 (APM): 2 (15) Control (No ATM): 1 (8) Other I1 (OAC): 2 (17) I2 (APM): 1 (8) Control (No ATM): 2 (15) Groups comparable at baseline? no			N (%) Reasons (describe) Control: N (%) Reasons (describe)	I2 (APM): 6 Control (No ATM): 2 Incidence per patient year: I1 (OAC): 10.2 I2 (APM): 9.4 Control (No ATM): 5.6 Incidence ratio (when compared to no ATM): (95%CI): I1 (OAC): 1.8 (0.3-12.9) I2 (APM): 1.7 (0.3-8.3)	
GIB							
Witt, 2012	Type of study: Retrospective cohort study	<u>Inclusion criteria</u>: hospitalized/emergency care encounter for **GIB**, outpatient purchase of warfarin and INR in 60 days before GIB, KPCO membership,	Resumption of warfarin (or continuation)	No resumption warfarin	<u>Length of follow-up</u>: 90 days	I vs. C <u>Thrombotic event</u> (arterial: stroke (n=5), systemic embolus	Patients who never stopped warfarin are included in the reinitiation group (n=41) Median time to resumption of warfarin was 4 days (2-9 days)/

	Setting: hospital Country: US Source of funding: CSL Behring LLC provided funding for the study	no GIB during 6 months before index GIB <u>Exclusion criteria</u>: - <u>N total at baseline</u>: 442 Intervention: 260 Control: 182 <u>Important prognostic factors</u>: *age ± SD:* *I: 71.8±12.0* *C: 77.7±11.3* *Sex:* *I: 49.6% M* *C: 51.1% M* *Indication for anticoagulation therapy:* AF: I: 46.2% C: 56.6%, p=0.03 VTE: I: 25.8% C: 22.5%, [=0.44 Prostetic heart valve: I: 15.4% C: 1.1%, p<0.001 Other: I: 12.7% C: 19.8%, p=0.04 *GIB location* Large intestine: I: 28.1% C: 23.6%, p=0.26 Mouth-esophagus:			<u>Loss-to-follow-up</u>: - <u>Incomplete outcome data</u>: -	(n=1), venous: PR (n=3), DVT (2): 1 (0.04%) vs. 10 (5.5%), p<0.001 HR 0.05 95%-CI: 0.01-0.58 <u>Recurrent GIB</u> 26 (10.0%) vs. 10 (5.5%), p=0.09 Multivariable analysis: HR 1.32 95%-CI: 0.50-3.57] <u>Deceased</u> 15 (5.8%) vs. 37 (20.3%) P<0.001 Multivariable analysis: HR 0.31 95%-CI 0.15-0.62) Analysis excluding deceased within 1 week: association remained	Multivariate analysis was corrected for: controlled for propensity score, CDS, age, sex, indication for warfarin use, prior heart failure diagnosis, location of GIB, pre-FIB target INR, pre-GIB percentage of INR in range, reception of LMWH, length of ED/inpatient stay, acute GIB treatment Compared with all other patients the rate of recurrent GIB was sign increased when warfarin therapy was resumed between 1 and 7 days after GIB (6.23% vs. 12.4%, p=0.03). Most common causes of death: related to malignancy (28.8%), infection (19.2%), cardiac disease (17.3%). No recurrent GIB resulted in death

		I: 7.7% C: 5.5%, p=0.37 Rectum-anus: I: 19.6% C: 7.1%, p<0.01 Small-intestine: I: 2.7% C: 3.9%, p=0.50 Stomach-duodenum: I: 25.0% C: 32.7%, p=0.07 Not identified: I: 16.9% C: 26.9%, p=0.01 Groups comparable at baseline? No, prostetic heart valve and GIB localized to rectum-anus were more common in I group					
Sengupta, 2015	Type of study: prospective observational cohort Setting: Single setting (hospital) Country: US Source of funding: none	Inclusion criteria: GIB while on systemic anticoagulation (clinically significant **GIB**: overt hematochezia, hematemesis, melena, guaiac-positive stools, with sign. Drop in haemoglobin). Exclusion criteria:- N total at baseline: 208 (excluded: 11) Intervention: 121 Control:76 Important prognostic factors[2]: Age, median (IQR), years: *I:* 75 (64,82) C:77 (66,84), p=0.32	Anticoagulation Resumed (n=121)	Anticoagulation Stopped (n=76)	Length of follow-up: 90 days Loss-to-follow-up: 12% I: 8171 (11%) person-days C: 4295 (14%) person-days of follow-up P=0.50	I vs. C Thromboembolic event venous thromboembolism (pulmonary embolism or deep vein thrombosis (DVT)), arterial thromboembolism, stroke, or transient ischemic attack. 1 (0.8%) vs, 6 (8%), p=0.003	At hospital discharge, the decision to resume or discontinue anticoagulation was made by the physicians directly responsible for patient care, depending on clinician and patient preferences. We categorized patients into whether anticoagulation was resumed or whether there was interruption of anticoagulation. Interruption of anticoagulation was defined as holding systemic anticoagulation for 72 h or more after discharge. Analyses were adjusted for the following factors included in the propensity score: age,

		Sex: *I: 55% M* *C: 62% M, p=0.38* *Indication for anticoagulation* I vs. C, p Atrial fibrillation: I: 71 (59%) C: 44 (58%), p=1.00 History DVT: I: 23 (19%) C: 13 (17%), p=0.85 History PE: I: 17 (14%) C: 5 (7%), p=0.16 Prosthetic valve: I: 18 (15%) C: 0 (0%), p=0.000 Portal vein thrombosis: I: 2 (2%) C: 4 (5%), p=0.21 Post surgical procedure: I: 1 (1%) 2 C: (3%), p=0.56 *Cause of GIB* Esophagitis I: 4 (3%) C: 2 (3%), p=1.00 Gastric ulcer I: 8 (7%) C: 7 (9%), p=0.58 Gastritis I: 8 (7%) C: 3 (4%), p=0.53 Dieulafoy's I: 5 (4%)			<u>Incomplete outcome data</u>: Patients who died during initial hospitalizati on were excluded from statistical analysis n=11 (5%)	HR multivariate analysis controlling for propensity score: 0.121, 95%-CI=0.006–0.812 <u>Recurrent GIB</u> readmission to any hospital in the 90-day follow-up period because of another episode of GIB HR=2.17, 95% CI=0.861–6.67, P =0.10 Importantly, there were no deaths in this group of patients readmitted with GIB. <u>Mortality:</u> HR multivariate analysis: HR=0.632, 95% CI=0.216–1.89, P =0.40	gender, Charlson comorbidity index, transfusion requirements, and active malignancy. After excluding the patients who restarted systemic anticoagulation because of having a thromboembolic episode in follow-up, 15 (20%) of the original 76 patients in the anticoagulation interruption cohort had restarted anticoagulation by the 90-day follow-up call. In these patients, anticoagulation was restarted at a median of 25 days from initial discharge. None of the 15 patients who restarted anticoagulation in follow-up were readmitted to the hospital within 90 days because of recurrent GIB. No raw data for recurrent GIB and mortality In summary, we found that resuming anticoagulation aft er hospitalization for GIB was associated with a signifi cantly decreased adjusted risk of major thromboembolic events over 90 days, without a signifi cantly increased risk of recurrent GIB. Th ese data support the recommendation that anticoagulation should be continued aft er an episode of GIB whenever possible.

		C: 2 (3%), p=0.71 AVMs I: 15 (12%) C: 3 (4%), p=0.07 Duodenal ulcer I: 5 (4%) C: 6 (8%), p=0.34 Diverticulosis I: 6 (5%) C: 10 (13%), p=0.06 Colonic ulcer I: 3 (2%) C: 2 (3%), p=1.0 Hemorrhoids I: 5 (4%) C: 1 (1%), p=0.41 Other (ischemic colitis 3, Mallory Weiss Tear 3,GAVE 1 duodenitis 3) I: 6 (5%) C: 4 (5%), p=1.00 Colitis I: 2 (2%) C:4 (5%), p=0.21 Post polypectomy I: 6 (5%) C: 2 (3%), p=0.71 Radiation proctitis I: 4 (3%) C: 2 (3%), p=1.00 Source not identified I: 45 (37%) C: 27 (36%), p=0.88 *Management* No blood transfusion I: 49 (40%) C: 24 (32%), p=0.23					

		No vitamin K I: 66 (55%) C: 46 (61%), p=0.46 No FFP I: 74 (61%) C: 48 (63%), p=0.88 ICU care I: 54 (45%) C: 37 (49%), p=0.66 Endoscopic intervention I: 26 (21%) C: 13 (17%), p=0.58 Groups comparable at baseline? Intervention group: more prostetic valves, prior stroke or TIA, or prior GIB. C group: more likely to have history of active malignancy.					
Qureshi, 2014	Type of study: Retrospecti ve cohort Setting: Hospital Country: US Source of funding: department of internal medicine of henry ford health system	<u>Inclusion criteria</u>: Patients who developed major **GIB** while taking warfarin and then had evidence of resolution of major GIB (defined as stability of hemoglobin levels with <1 g decrease of hemoglobin for 48 hours) <u>Exclusion criteria</u>: pts who died <72h of GIB, hospice, postoperative or valvular AF, patients in whom primary indication for anticoagulation was any reason other than nonvalvular AF, warfarin was not interrupted for at least 48h	Restarting warfarin	Warfarin cessitation (or starting>6 months)	Length of follow-up: 2 years Loss-to-follow-up: Intervention : N (%) Reasons (describe) Control: N (%) Reasons (describe)	I vs. C <u>Recurrent major GIB (<90 days)</u> defined as any of the following: (1) >2 g of hemoglobin decrease from the last known hemoglobin level warranting hospitalization, (2) need for blood transfusion of at least 2 units, and (3) visible bleeding by health personnel or endoscopic evidence of	GIB was defined as a decrease in hemoglobin of 2 g/dl and/or transfusion of 2 units of packed red blood cells with at least one of the following: hematemesis, melena, hematochezia, bright red blood per rectum, blood in nasogastric aspirate, or bleeding documented during an endoscopic procedure. Restarting warfarin was defined as prescription of warfarin with objective evidence of increase in international normalized ratio to 2.0 with evidence of at least 2 days of discontinuation of warfarin as observed by chart review. Patients who interrupted warfarin after 1 month of restarting warfarin

		N total at baseline: 1329 Intervention: 653 Control:676 Important prognostic factors[2]: *age ± SD:* *I: 74.8±10.7* *C:75.3±10.7, p=0.43* *Sex:* *I: 55.7% M* *C: 49.7% M, p=0.03* Groups comparable at baseline? Caucasians, patients with concomitant upper and lower sources for GIB, diabetics, patients with renal disease, history of coronary artery disease, and history of falls were less likely to be restarted on warfarin (p <0.05). Overall, there were greater co-morbidity burdens in the patients who were not restarted on warfarin. Major reasons for not restarting warfarin were physician preference (18%) and patient's inability to follow up with the anticoagulation clinic (19%).			Incomplete outcome data: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe)	stigmata of recent bleeding in the form of visible bleeding or clot. Adjusted Hazard Ratio (95% CI): 0.71 (0.54-0.93), p=0.01 Thromboembolism (1 year) defined as venous thromboembolism (pulmonary embolism and deep venous thrombosis), arterial thromboembolism, or stroke or transient ischemic attack. Adjusted Hazard Ratio (95% CI): 0.71 (0.54-0.93), p=0.01 Mortality Adjusted hazard ratio 0.66, 95% confidence interval 0.56 to 0.81, p <0.0001	(54; 4.1%) were included in the group that restarted warfarin. Patients who started warfarin after 6 months of interruption (39, 2.9%) were included in the group that did not restart warfarin (warfarin cessation group). Patients who interrupted warfarin within the first month (12; 0.9%) were included in the warfarin cessation group. Multivariate analysis were adjusted for age, gender, race, Charlson co-morbidity index, number of blood product transfusions, international normalized ratio on admission, and CHADS2 and HAS-BLED scores
Traumatisch hersenletsel							
Albrecht, 2014	Type of study: Retrospective analysis insurance	Inclusion criteria:medicare benificiaries, >65yrs, hospitalized for traumatic brain injury (2006-2009) who received warfarin in the month prior to the injury (for: AF).	Warfarin (or other anticoagulant) resumption	No resumption	Length of follow-up: Mean (SD) length of follow-up	Trombotic event, n, incidence rate (per 1000) I: n=400, 113.5 (95%CI: 102.9-125.2)	The final model for hemorrhagic outcomes included the following time-invariant and time-varying variables: age, sex,

	beneficiaries Setting: hospital Country: USA Source of funding: none reported	<u>Exclusion criteria</u>: <u>N total at baseline</u>: 10 782 I1: 1877 I2: 3934 C: 4971 <u>Important prognostic factors</u>[2]: *age ± SD:* I1: 81.0 (7.4) I2: 80.1 (7.2) C: 82.4 (7.3) *Sex: n male (%)* I1: 691 (37) I2: 1323 (34) C: 1836 (37) Atrial fibrillation: I1:1532 (82) I2:3333 (85) C: 3978 (80) p<.001 CHADs2 score >2, No. (%) I1: 1577 (84) I2: 3197 (81) C: 4223 (85) p<.001 Modified HEMORR2HAGES score >3, No. (%) I1: 1141 (61) I2: 2093 (53) C: 2994 (60) p<.001 Groups comparable at baseline? No, Beneficiaries differed by warfarin use categories (Table 1).	I1: for 1-6 months I2: 7-12 months		after discharge from hospitalization for TBI was 594.9 (405.6) days <u>Loss-to-follow-up</u>: - <u>Incomplete outcome data</u>: I1: 719 (38%) I2: 1205 (31%) C: 2358 (47%) Control: N (%) Reasons (describe) Patients transferred to skilled nursing facility (SNF) have missing values for warfarin use	C: 562, 155.9 (143.5-169.3) RR 0.77 [0.67-0.88] Hemorrhagic event, n, incidence rate (per 1000): I: 422, 119.8 (108.9-131.8) C: 309 85.7 (76.7-95.8) RR: 1.51 (1.29-1.78) Hemorrhagic or ischemic stroke, n, incidence rate (per 1000): I: 339, 96.2 (87.5-105.8) C: 494, 137.0 (122.6-153.2) RR: 0.83 (0.72-0.96) The interaction between period and lagged warfarin use was not statistically significant; therefore, the regression results are interpreted as the effect of the lagged warfarin use variable on outcomes averaged over the first 12 periods following discharge from hospitalization for TBI.	race, pre-TBI hemorrhagic event, lagged warfarin use, period (continuous), other anticoagulant use in the period, length of hospital stay (categorical), discharge to SNF, atrial fibrillation, liver disease, chronic kidney disease, ethanol abuse, malignant neoplasm, hypertension, anemia, coagulation defect, neurological disease, and thrombotic event in the period. The final model for thrombotic outcomes included the following time-invariant and time-varying variables: age, sex, race, pre-TBI thrombotic event, lagged warfarin use, hemorrhagic event in the period, period (continuous), other anticoagulant use in the period, length of hospital stay (categorical), discharge to SNF, stroke or transient ischemic attack, hypertension, diabetes mellitus, and heart failure. Restricting our analyses to patients with atrial fibrillation did not significantly affect estimates of the effect of warfarin receipt.

		Beneficiaries who used warfarin for 7 to 12months (mean [SD] age, 80.1 [7.2] years) were younger than those who used warfarin for 1 to 6 months (mean [SD] age, 81.0 [7.4] years) and thosewhodid not use warfarin (mean [SD] age, 82.4 [7.3] years; analysis of variance P < .001). They were less likely to have a hospital stay of 9 ormore days (15%vs 17%vs 28%; P < .001). Beneficiaries who used warfarin for 7 to 12 months were less likely to have Alzheimer disease and related dementias (27% vs 35% vs 39%; P < .001).			(other payment):		

Quality assessment table: herstarten antistolling na bloeding

Study reference **(first author, year of publication)**	**Bias due to a non-representative or ill-defined sample of patients?** **(unlikely/likely/unclear)**	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?** **(unlikely/likely/unclear)**	**Bias due to ill-defined or inadequately measured outcome?** **(unlikely/likely/unclear)**	**Bias due to inadequate adjustment for all important prognostic factors?** **(unlikely/likely/unclear)**
ICH				
Majeed, 2010	Likely (reasons for restarting therapy are not described, but likely that the factors for restarting are also prognostic factors; therefore likely to cause bias).	Unlikely	Unlikely	Unlikely
Gathier, 2013	Likely (reasons for restarting therapy are likely also prognostic factors; therefore likely to cause bias).	Unlikely	Unlikely	Likely (not all relevant prognostic factors were corrected for / available)
Yung, 2012	Likely (reasons for restarting therapy are likely also prognostic factors; therefore likely to cause bias).	Unclear (retrospective, not fully clear how long follow-up was)	Unlikely	Likely (not all relevant prognostic factors were available from registration)
GIB				

Witt, 2012	Likely (reasons for restarting therapy are likely also prognostic factors; therefore likely to cause bias).	Unlikely	Unlikely	Unlikely
Sengupta, 2015	Likely (reasons for restarting therapy are likely also prognostic factors; therefore likely to cause bias).	Unlikely (relatively high loss-to-follow-up, however comparable in both groups)	Unlikely	Unlikely
Qureshi, 2014	Likely (reasons for restarting therapy are likely also prognostic factors; therefore likely to cause bias).	Unlikely	Unlikely	Likely (not all relevant prognostic factors were corrected for / available)
TBI				
Albrecht, 2014	Likely (reasons for restarting therapy are likely also prognostic factors; therefore likely to cause bias).	Likely, patients transferred to skilled nursing facility (SNF) have missing values for warfarin use (other payment). Incomplete data differs for groups.	Unlikely	Unlikely

Table of excluded studies

Initial search

Reference	Reason for exclusion
Poli D, Antonucci E, Dentali F, Erba N, Testa S, Tiraferri E, et al. Recurrence of ICH after resumption of anticoagulation with VK antagonists: CHIRONE study. Neurology. 2014;82(12):1020-6	No comparative study; wrong outcome (only recurrence)
Pasquini M, Charidimou A, van Asch CJ, Baharoglu MI, Samarasekera N, Werring DJ, et al. Variation in restarting antithrombotic drugs at hospital discharge after intracerebral hemorrhage. Stroke. 2014;45(9):2643-8	Wrong study design (descriptive analysis)
Chari A, Clemente Morgado T, Rigamonti D. Recommencement of anticoagulation in chronic subdural haematoma: a systematic review and meta-analysis. Br J Neurosurg. 2014;28(1):2-7.	Wrong study population
Hawryluk GW, Austin JW, Furlan JC, Lee JB, O'Kelly C, Fehlings MG. Management of anticoagulation following central nervous system hemorrhage in patients with high thromboembolic risk. J Thromb Haemost. 2010;8(7):1500-8	Wrong study design (also included case reports)

5 **Updated search**

Reference	Reason for exclusion
Barra ME, Forman R, Long-Fazio B, Merkler AE, Gurol ME, Izzy S, Sharma R. Optimal Timing for Resumption of Anticoagulation After Intracranial Hemorrhage in Patients With Mechanical Heart Valves. J Am Heart Assoc. 2024 May 21;13(10):e032094. doi: 10.1161/JAHA.123.032094. Epub 2024 May 18. PMID: 38761076; PMCID: PMC11179836.	Small cohort (N<500)
Brouillard P, Diallo EH, Masson JB, Raymond JM, Riahi M, Potter B, Kouz R, Potvin J. Real-World Management Strategies of Anticoagulated Atrial Fibrillation Patients After a Clinically Significant Bleeding Episode. Can J Cardiol. 2024 Jul;40(7):1283-1290. doi: 10.1016/j.cjca.2023.12.032. Epub 2024 Jan 4. PMID: 38181972.	Small cohort (N<500)
Gennaro N, Ferroni E, Zorzi M, Denas G, Pengo V. ISCHEMIC STROKE AND MAJOR BLEEDING WHILE ON DIRECT ORAL ANTICOAGULANTS IN NAÏVE PATIENTS WITH ATRIAL FIBRILLATION: IMPACT OF RESUMPTION OR DISCONTINUATION OF ANTICOAGULANT TREATMENT. A population-based study. Int J Cardiol. 2024 Jan 1;394:131369. doi: 10.1016/j.ijcard.2023.131369. Epub 2023 Sep 16. PMID: 37722453.	Not in agreement with PICO (wrong outcome)
Kuramatsu JB, Sembill JA, Gerner ST, Sprügel MI, Hagen M, Roeder SS, Endres M, Haeusler KG, Sobesky J, Schurig J, Zweynert S, Bauer M, Vajkoczy P, Ringleb PA, Purrucker J, Rizos T, Volkmann J, Müllges W, Kraft P, Schubert AL, Erbguth F, Nueckel M, Schellinger PD, Glahn J, Knappe UJ, Fink GR, Dohmen C, Stetefeld H, Fisse AL, Minnerup J, Hagemann G, Rakers F, Reichmann H, Schneider H, Wöpking S, Ludolph AC, Stösser S, Neugebauer H, Röther J, Michels P, Schwarz M, Reimann G, Bäzner H, Schwert H, Claßen J, Michalski D, Grau A, Palm F, Urbanek C, Wöhrle JC, Alshammari F, Horn M, Bahner D, Witte OW, Günther A, Hamann GF, Lücking H, Dörfler A, Achenbach S, Schwab S, Huttner HB. Management of therapeutic anticoagulation in patients with intracerebral haemorrhage and mechanical heart valves. Eur Heart J. 2018 May	Not in agreement with PICO (wrong comparison); small study (N<500)

14;39(19):1709-1723. doi: 10.1093/eurheartj/ehy056. PMID: 29529259; PMCID: PMC5950928.	
Li L, Poon MTC, Samarasekera NE, Perry LA, Moullaali TJ, Rodrigues MA, Loan JJM, Stephen J, Lerpiniere C, Tuna MA, Gutnikov SA, Kuker W, Silver LE, Al-Shahi Salman R, Rothwell PM. Risks of recurrent stroke and all serious vascular events after spontaneous intracerebral haemorrhage: pooled analyses of two population-based studies. Lancet Neurol. 2021 Jun;20(6):437-447. doi: 10.1016/S1474-4422(21)00075-2. Erratum in: Lancet Neurol. 2021 Aug;20(8):e5. doi: 10.1016/S1474-4422(21)00185-X. PMID: 34022170; PMCID: PMC8134058.	Not in agreement with PICO
Liu CH, Wu YL, Hsu CC, Lee TH. Early Antiplatelet Resumption and the Risks of Major Bleeding After Intracerebral Hemorrhage. Stroke. 2023 Feb;54(2):537-545. doi: 10.1161/STROKEAHA.122.040500. Epub 2023 Jan 9. PMID: 36621820.	Not in agreement with PICO
Meyre PB, Blum S, Hennings E, Aeschbacher S, Reichlin T, Rodondi N, Beer JH, Stauber A, Müller A, Sinnecker T, Moutzouri E, Paladini RE, Moschovitis G, Conte G, Auricchio A, Ramadani A, Schwenkglenks M, Bonati LH, Kühne M, Osswald S, Conen D. Bleeding and ischaemic events after first bleed in anticoagulated atrial fibrillation patients: risk and timing. Eur Heart J. 2022 Dec 14;43(47):4899-4908. doi: 10.1093/eurheartj/ehac587. PMID: 36285887.	Not in agreement with PICO (no comparison)
Murphy MP, Kuramatsu JB, Leasure A, Falcone GJ, Kamel H, Sansing LH, Kourkoulis C, Schwab K, Elm JJ, Gurol ME, Tran H, Greenberg SM, Viswanathan A, Anderson CD, Schwab S, Rosand J, Shi FD, Kittner SJ, Testai FD, Woo D, Langefeld CD, James ML, Koch S, Huttner HB, Biffi A, Sheth KN. Cardioembolic Stroke Risk and Recovery After Anticoagulation-Related Intracerebral Hemorrhage. Stroke. 2018 Nov;49(11):2652-2658. doi: 10.1161/STROKEAHA.118.021799. PMID: 30355194; PMCID: PMC6211810.	Not in agreement with PICO (wrong outcomes)
Naylor RM, Dodin RE, Henry KA, De La Peña NM, Jarvis TL, Labott JR, Van Gompel JJ. Timing of Restarting Anticoagulation and Antiplatelet Therapies After Traumatic Subdural Hematoma-A Single Institution Experience. World Neurosurg. 2021 Jun;150:e203-e208. doi: 10.1016/j.wneu.2021.02.135. Epub 2021 Mar 5. PMID: 33684586.	Not in agreement with PICO (wrong population)
Nielsen PB, Melgaard L, Overvad TF, Jensen M, Larsen TB, Lip GYH; PRESTIGE-AF Consortium. Risk of Cerebrovascular Events in Intracerebral Hemorrhage Survivors With Atrial Fibrillation: A Nationwide Cohort Study. Stroke. 2022 Aug;53(8):2559-2568. doi: 10.1161/STROKEAHA.121.038331. Epub 2022 Apr 13. PMID: 35414198; PMCID: PMC9311292.	Not in agreement with PICO (wrong comparison)
Pappas MA, Burke JF. Net clinical benefit of anticoagulation for atrial fibrillation following intracerebral hemorrhage. Vasc Med. 2020 Feb;25(1):55-59. doi: 10.1177/1358863X19883027. Epub 2020 Jan 13. PMID: 31928394.	Prediction model, not in agreement with PICO
Peng D, Zhai H. Application of Antithrombotic Drugs in Different Age-Group Patients with Upper Gastrointestinal Bleeding. Gastroenterol Res Pract. 2024 Apr 4;2024:1710708. doi: 10.1155/2024/1710708. PMID: 38606387; PMCID: PMC11008970.	Not in agreement with PICO (wrong outcomes)
Perino AC, Kaiser DW, Lee RJ, Fan J, Askari M, Schmitt SK, Turakhia MP. Incidence and outcomes of patients with atrial fibrillation and major bleeding complications: from the TREAT-AF study. J Interv	Not in agreement with PICO (wrong population)

Card Electrophysiol. 2021 Oct;62(1):133-142. doi: 10.1007/s10840-020-00873-0. Epub 2020 Sep 28. PMID: 32986177.	
Rigual R, Rodríguez-Pardo J, Lorenzo-Diéguez M, Fernández-Fernández S, Torres Iglesias G, Lastras C, Ruiz-Ares G, de Leciñana MA, de Celis E, Casado-Fernández L, Hervás C, Alonso E, Díez-Tejedor E, Fuentes B. Keeping prior anticoagulation treatment in the acute phase of ischaemic stroke: the REKOALA study. J Neurol. 2024 Jul;271(7):4086-4094. doi: 10.1007/s00415-024-12204-8. Epub 2024 Apr 5. PMID: 38578495; PMCID: PMC11233373.	Not in agreement with PICO (wrong population)
Salih M, Young M, Shutran M, Stippler M, Papavassiliou E, Alterman RL, Thomas AJ, Taussky P, Moore J, Ogilvy CS. Effect of long-term anticoagulant therapy on the outcome of chronic subdural hematoma: a propensity score-matched analysis. J Neurosurg. 2022 Dec 23;139(1):194-200. doi: 10.3171/2022.11.JNS222022. PMID: 36681947.	Not in agreement with PICO (wrong population)
Vestergaard AS, Skjøth F, Lip GY, Larsen TB. Effect of Anticoagulation on Hospitalization Costs After Intracranial Hemorrhage in Atrial Fibrillation: A Registry Study. Stroke. 2016 Apr;47(4):979-85. doi: 10.1161/STROKEAHA.115.012338. Epub 2016 Feb 16. PMID: 26883499.	Overlapping population with Nielsen, 2017
Winijkul A, Kaewkumdee P, Yindeengam A, Lip GYH, Krittayaphong R. Clinical Outcomes of Patients with Atrial Fibrillation who Survived from Bleeding Event: The Results from COOL-AF Thailand Registry. Thromb Haemost. 2024 Apr 16. doi: 10.1055/s-0044-1786028. Epub ahead of print. PMID: 38626898.	Not in agreement with PICO (wrong comparison)
Cheng B, Li J, Peng L, Wang Y, Sun L, He S, Wei J, Zhang S. Efficacy and safety of restarting antiplatelet therapy for patients with spontaneous intracranial haemorrhage: A systematic review and meta-analysis. J Clin Pharm Ther. 2021 Aug;46(4):957-965. doi: 10.1111/jcpt.13377. Epub 2021 Feb 4. PMID: 33537999.	Includes studies not compliant with PICO
Huang XY, Zhang JY, Yu CY. Whether it is safe to start anticoagulation after intracranial hemorrhage within 2 weeks: A systematic review and meta-analysis. Ibrain. 2022 Aug 19;8(3):377-388. doi: 10.1002/ibra.12060. PMID: 37786745; PMCID: PMC10528763.	Includes studies not compliant with PICO
Liu M, Hou Y, Liu W, Liu M. Effect of oral anticoagulation therapy in atrial fibrillation patients with a history of intracranial hemorrhage: a systematic review and meta-analysis. Ann Palliat Med. 2022 Oct;11(10):3063-3074. doi: 10.21037/apm-22-582. Epub 2022 Aug 8. PMID: 35948473.	Includes studies not compliant with PICO
Tapaskar N, Pang A, Werner DA, Sengupta N. Resuming Anticoagulation Following Hospitalization for Gastrointestinal Bleeding Is Associated with Reduced Thromboembolic Events and Improved Mortality: Results from a Systematic Review and Meta-Analysis. Dig Dis Sci. 2021 Feb;66(2):554-566. doi: 10.1007/s10620-020-06248-9. Epub 2020 Apr 11. PMID: 32279174.	Includes studies not compliant with PICO
Zhao J, Wu X, Li S, Gu Q. Effectiveness and safety of oral anticoagulant therapy in patients with atrial fibrillation with prior gastrointestinal bleeding: A systematic review and meta-analysis. Front Cardiovasc Med. 2022 Jul 27;9:937320. doi: 10.3389/fcvm.2022.937320. PMID: 35966547; PMCID: PMC9363568.	Includes studies not compliant with PICO
Zhou Q, Liu X, Yang X, Huang XH, Wu YZ, Tao YY, Wei M. Efficacy and safety of anticoagulation in atrial fibrillation patients with intracranial hemorrhage: A systematic review and meta-analysis.	Includes studies not compliant with PICO

Front Pharmacol. 2023 Mar 9;14:1122564. doi: 10.3389/fphar.2023.1122564. PMID: 36969833; PMCID: PMC10033967.	
Zhou Y, Guo Y, Liu D, Feng H, Liu J. Restarting of anticoagulation in patients with atrial fibrillation after major bleeding: A meta-analysis. J Clin Pharm Ther. 2020 Aug;45(4):591-601. doi: 10.1111/jcpt.13130. Epub 2020 Mar 17. PMID: 32181518.	Includes studies not compliant with PICO
Cai H, Chen G, Hu W, Jiang C. Anticoagulant in atrial fibrillation patients with prior intracranial haemorrhage: a meta-analysis. Heart. 2023 Oct 12;109(21):1594-1600. doi: 10.1136/heartjnl-2023-322492. PMID: 37321829.	Includes studies not compliant with PICO
Hu W, Cai H, Zhang J. Direct oral anticoagulants versus warfarin in nonvalvular atrial fibrillation patients with prior gastrointestinal bleeding: a network meta-analysis of real-world data. Eur J Clin Pharmacol. 2022 Jul;78(7):1057-1067. doi: 10.1007/s00228-022-03300-7. Epub 2022 Mar 16. PMID: 35296907.	Includes studies not compliant with PICO
Bingzheng X, Jingnan R, Ligang B, Jianping C. The effects of anticoagulant therapy re-initiation after gastrointestinal bleeding: A systematic review and meta-analysis. J Clin Pharm Ther. 2021 Dec;46(6):1509-1518. doi: 10.1111/jcpt.13442. Epub 2021 Jun 7. PMID: 34101229.	Includes studies not compliant with PICO
Chi G, Lee JJ, Sheng S, Marszalek J, Chuang ML. Systematic Review and Meta-Analysis of Thromboprophylaxis with Heparins Following Intracerebral Hemorrhage. Thromb Haemost. 2022 Jul;122(7):1159-1168. doi: 10.1055/s-0042-1744541. Epub 2022 Jun 19. PMID: 35717948.	Includes studies not compliant with PICO
Edlmann E, Maripi H, Whitfield P. Systematic review on traumatic intracranial haemorrhage in patients on anti-thrombotic medications; haemorrhage progression, thrombosis, and anti-thrombotic recommencement. Neurosurg Rev. 2023 Jul 6;46(1):166. doi: 10.1007/s10143-023-02075-4. PMID: 37410188.	Includes studies not compliant with PICO
Hashash JG, Aoun R, El-Majzoub N, Khamis A, Rockey D, Akl EA, Barada K. Resuming aspirin in patients with non-variceal upper gastrointestinal bleeding: a systematic review and meta-analysis. Ann Gastroenterol. 2021;34(3):344-353. doi: 10.20524/aog.2021.0617. Epub 2021 Mar 23. PMID: 33948059; PMCID: PMC8079865.	Includes studies not compliant with PICO
Milling TJ Jr, Warach S, Johnston SC, Gajewski B, Costantini T, Price M, Wick J, Roward S, Mudaranthakam D, Dula AN, King B, Muddiman A, Lip GYH. Restart TICrH: An Adaptive Randomized Trial of Time Intervals to Restart Direct Oral Anticoagulants after Traumatic Intracranial Hemorrhage. J Neurotrauma. 2021 Jun 1;38(13):1791-1798. doi: 10.1089/neu.2020.7535. Epub 2021 Apr 6. PMID: 33470152; PMCID: PMC8219199.	Includes studies not compliant with PICO
Al-Shahi Salman R, Stephen J, Tierney JF, Lewis SC, Newby DE, Parry-Jones AR, White PM, Connolly SJ, Benavente OR, Dowlatshahi D, Cordonnier C, Viscoli CM, Sheth KN, Kamel H, Veltkamp R, Larsen KT, Hofmeijer J, Kerkhoff H, Schreuder FHBM, Shoamanesh A, Klijn CJM, van der Worp HB; Collaboration of Controlled Randomised Trials of Long-Term Oral Antithrombotic Agents After Spontaneous Intracranial Haemorrhage (COCROACH). Effects of oral anticoagulation in people with atrial fibrillation after spontaneous intracranial haemorrhage (COCROACH): prospective, individual participant data meta-analysis of randomised trials. Lancet Neurol. 2023 Dec;22(12):1140-1149. doi: 10.1016/S1474-4422(23)00315-0. Epub 2023 Oct 12. PMID: 37839434.	Includes studies not compliant with PICO

Brannigan JFM, Gillespie CS, Adegboyega G, Watson M, Lee KS, Mazzoleni A, Goacher E, Mantle O, Omar V, Gamage G, Yanez Touzet A, Mowforth O, Thomas W, Uprichard J, Hutchinson PJ, Stubbs DJ, Davies BM; ICENI Working Group. Impact of antithrombotic agents on outcomes in patients requiring surgery for chronic subdural haematoma: a systematic review and meta-analysis. Br J Neurosurg. 2024 Apr 8:1-8. doi: 10.1080/02688697.2024.2333399. Epub ahead of print. PMID: 38584489.	Includes studies not compliant with PICO
RESTART Collaboration. Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial. Lancet. 2019 Jun 29;393(10191):2613-2623. doi: 10.1016/S0140-6736(19)30840-2. Epub 2019 May 22. PMID: 31128924; PMCID: PMC6617509.	Not in agreement with PICO
Al-Shahi Salman R, Dennis MS, Sandercock PAG, Sudlow CLM, Wardlaw JM, Whiteley WN, Murray GD, Stephen J, Rodriguez A, Lewis S, Werring DJ, White PM; RESTART Collaboration. Effects of Antiplatelet Therapy After Stroke Caused by Intracerebral Hemorrhage: Extended Follow-up of the RESTART Randomized Clinical Trial. JAMA Neurol. 2021 Oct 1;78(10):1179-1186. doi: 10.1001/jamaneurol.2021.2956. PMID: 34477823; PMCID: PMC8417806.	Not in agreement with PICO
Schreuder FHBM, van Nieuwenhuizen KM, Hofmeijer J, Vermeer SE, Kerkhoff H, Zock E, Luijckx GJ, Messchendorp GP, van Tuijl J, Bienfait HP, Booij SJ, van den Wijngaard IR, Remmers MJM, Schreuder AHCML, Dippel DW, Staals J, Brouwers PJAM, Wermer MJH, Coutinho JM, Kwa VIH, van Gelder IC, Schutgens REG, Zweedijk B, Algra A, van Dalen JW, Jaap Kappelle L, Rinkel GJE, van der Worp HB, Klijn CJM; APACHE-AF Trial Investigators. Apixaban versus no anticoagulation after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation in the Netherlands (APACHE-AF): a randomised, open-label, phase 2 trial. Lancet Neurol. 2021 Nov;20(11):907-916. doi: 10.1016/S1474-4422(21)00298-2. PMID: 34687635.	Phase 2 trial

Literature search strategy

5 Zoekverantwoording

Initial search 2015

Database	Zoektermen	Totaal
Medline (OVID) 2010-feb. 2015	1 exp Anticoagulants/ (178764) 2 "Vitamin K"/ai or "Vitamin K"/tu or VKA.ti,ab. or "vitamin K".ti,ab. (10879) 3 (4-hydroxycoumarin* or warfarin*).ti,ab. (17077) 4 (heparin* or LMWH* or dalteparin* or enoxaparin* or nadroparin* or tinzaparin* or pentasacharide* or aspirin* or 'acetylsalicylic acid').ti,ab. or aspirin/ (127490) 5 (Rivaroxaban* or Dabigatran* or Apixaban* or Edoxaban* or ("New Oral Anticoagulant*" or "Novel Oral Anticoagulant*" or NOAC*)).ti,ab. (3645) 6 ("Direct Oral Anticoagulant*" or DOAC*).ti,ab. (149) 7 1 or 2 or 3 or 4 or 5 or 6 (266252)	196

	8 exp Hemorrhage/ (263928) 9 (H?emorrhage* or bleed*).ti,ab. (267496) 10 8 or 9 (410003) 11 7 and 10 (34250) 12 limit 11 to (yr="2010 -Current" and (dutch or english)) (8623) 17 (resum* or restart* or recommenc* or reinitiat*).ti,ab. (29302) 18 12 and 17 (158)	
Embase (Elsevier)	'anticoagulant agent'/exp/mj OR 'blood clotting inhibitor'/exp/mj OR 'low molecular weight heparin'/exp/mj OR heparin:ab,ti OR lmwh*:ab,ti OR dalteparin*:ab,ti OR enoxaparin*:ab,ti OR nadroparin*:ab,ti OR tinzaparin*:ab,ti OR pentasacharide*:ab,ti OR 'acetylsalicylic acid'/mj OR aspirin*:ab,ti OR 'acetylsalicylic acid':ab,ti OR rivaroxaban*:ab,ti OR dabigatran*:ab,ti OR apixaban*:ab,ti OR edoxaban*:ab,ti OR 'new oral anticoagulant':ab,ti OR 'new oral anticoagulants':ab,ti OR noac*:ab,ti OR 'novel oral anticoagulant':ab,ti OR 'novel oral anticoagulants':ab,ti OR 'direct oral anticoagulants':ab,ti OR 'direct oral anticoagulant':ab,ti OR doac*:ab,ti OR 'blood clotting factor 10a inhibitor'/exp/mj OR 'vitamin k antagonists' OR warfarin*:ab,ti OR coumarin*:ab,ti OR vka:ab,ti OR 'vitamin k antagonist':ab,ti OR 'vitamin k antagonists':ab,ti AND ('bleeding'/exp/mj OR bleed*:ab,ti OR h?emorrhag*) AND ([dutch]/lim OR [english]/lim) AND [embase]/lim AND [2010-2015]/py AND (resum*:ab,ti OR restart*:ab,ti OR recommenc*:ab,ti OR reinitiat*:ab,ti) NOT 'conference abstract':it, 155, 41 uniek	

Updated search 2024

Algemene informatie

Cluster/richtlijn: Antitrombotisch beleid - UV10 Herstarten van antistollingstherapie	
Uitgangsvraag/modules: Hoe moeten we omgaan met het herstarten van antistollingstherapie na een bloeding?	
Database(s): Embase.com, Ovid/Medline	Datum: 13 maart 2024
Periode: vanaf 2016	Talen: geen restrictie
Literatuurspecialist: Esther van der Bijl	Rayyan review: https://rayyan.ai/reviews/963048
BMI-zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht op de elementen: - patiënten met een bloeding - anticoagulation - herstarten anticoagulation	

→ De sleutelartikelen PMID34687635 en PMID31128924 worden gevonden met deze search. PMID34487722 wordt niet gevonden met deze search. Het artikel valt uit op zoekblok 'herstarten anticoagulation': er wordt in titel, abstract of keywords niet gesproken over herstarten.

Zoekopbrengst 13-3-2024

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SR	150	161	207
RCT	267	333	450
Observationeel	415	463	558
Totaal	832	957	**1215***

in Rayyan

5 ***Zoekopbrengst 28-1-2020***

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	29	28	36
RCTs	62	55	71
Overig	148	195	212
Totaal	239	278	319

Zoekstrategie Embase.com 13-3-2024

No.	Query	Results
#1	'bleeding'/exp/mj OR 'abdominal bleeding'/exp/mj OR 'brain hemorrhage'/exp/mj OR 'digestive system hemorrhage'/exp/mj OR 'respiratory tract hemorrhage'/exp/mj OR 'urinary tract hemorrhage'/exp/mj OR (((bleeding* OR haemorrhag* OR hemorrhag*) NEAR/3 (abnormal* OR abdom* OR brain* OR cerebral* OR 'corpus callosum' OR stroke* OR intracerebral* OR intracortical* OR intracranial OR intraventricul* OR periventricular* OR 'posterior fossa' OR alimentar* OR digestive* OR respirator* OR urinar*)):ti,ab,kw) OR encephalorrhagia:ti,ab,kw OR hematencephalon:ti,ab,kw	442457
#2	'thrombosis prevention'/exp OR 'anticoagulant agent'/exp OR 'anticoagulation'/exp OR 'anticoagulant therapy'/exp OR thromboprophyla*:ti,ab,kw OR ((thrombo* NEAR/3 (prophylaxis OR prophylactic OR prevention)):ti,ab,kw) OR 'anti coagulant*':ti,ab,kw OR 'anticoagulant*':ti,ab,kw OR 'anticoagulat*':ti,ab,kw OR 'anti coagulat*':ti,ab,kw OR 'antithrombotic*':ti,ab,kw OR 'anti thrombotic*':ti,ab,kw OR 'antithrombocytic*':ti,ab,kw OR 'anti	919129

	thrombocytic*':ti,ab,kw OR 'antiplatelet agent*':ti,ab,kw OR 'antiplatelet drug*':ti,ab,kw OR 'platelet aggregation inhibitor*':ti,ab,kw OR 'platelet inhibitor*':ti,ab,kw OR 'platelet antagonist*':ti,ab,kw OR 'thrombocyte aggregation inhibiting agent*':ti,ab,kw OR 'thrombocyte aggregation inhibitor*':ti,ab,kw OR 'direct oral anticoagulant agent'/exp OR 'direct oral anticoagulant'/exp OR doac*:ti,ab,kw	
#3	((bleeding* OR haemorrhag* OR hemorrhag*) NEAR/3 (anticoagulant* OR 'anti coagulant*' OR 'antithrombotic*')):ti,ab,kw	3974
#4	#1 AND #2 OR #3	67494
#5	resum*:ti,ab,kw OR restart*:ti,ab,kw OR recommenc*:ti,ab,kw OR reinitiat*:ti,ab,kw OR continua*:ti,ab,kw OR continue*:ti,ab,kw	884510
#6	#4 AND #5	4447
#7	#6 AND [2016-2024]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	1176
#8	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	1009437
#9	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3989646

#10	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	8118160
#11	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR	14898483

	compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#12	#7 AND #8 **- SR's**	150
#13	#7 AND #9 NOT #12 **– RCT's**	267
#14	#7 AND (#10 OR #11) NOT (#12 OR #13) **– Observationele studies**	415
#15	#12 OR #13 OR #14	832

Zoekstrategie Ovid/Medline 13-3-2024

#	Searches	Results
1	exp Hemorrhage/ or exp Intracranial Hemorrhages/ or exp Gastrointestinal Hemorrhage/ or ((bleeding* or haemorrhag* or hemorrhag*) adj3 (abnormal* or abdom* or brain* or cerebral* or corpus callosum or stroke* or intracerebral* or intracortical* or intracranial or intraventricul* or periventricular* or posterior fossa or alimentar* or digestive* or respirator* or urinar*)).ti,ab,kf. or encephalorrhagia.ti,ab,kf. or hematencephalon.ti,ab,kf.	418467
2	exp Anticoagulants/ or exp Platelet Aggregation Inhibitors/ or thromboprophyla*.ti,ab,kf. or (thrombo* adj3 (prophylaxis or prophylactic or prevention)).ti,ab,kf. or (anti coagulant* or anticoagulant* or anticoagulat* or anti coagulat* or antithrombotic* or anti thrombotic* or antithrombocytic* or anti thrombocytic* or 'antiplatelet agent*' or 'antiplatelet drug*' or 'platelet aggregation inhibitor*' or 'platelet inhibitor*' or platelet antagonist* or 'thrombocyte aggregation inhibiting agent*' or 'thrombocyte aggregation inhibitor*' or doac*).ti,ab,kf.	439948
3	((bleeding* or haemorrhag* or hemorrhag*) adj3 (anticoagulant* or anti coagulant* or antithrombotic*)).ti,ab,kf.	2513
4	(1 and 2) or 3	45609
5	(resum* or restart* or recommenc* or reinitiat* or continua* or continue*).ti,ab,kf.	614562
6	4 and 5	2685
7	limit 6 to yr="2016 -Current"	1333
8	7 not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)	1273
9	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*")	732082

	and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	
10	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2701090
11	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4675029
12	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5643187

13	8 and 9 **- SR's**	161
14	(8 and 10) not 13 **– RCT's**	333
15	(8 and (11 or 12)) not (13 or 14) **– Observationele studies**	463
16	13 or 14 or 15	957

Zoekverantwoording 28-1-2020

Database	Zoektermen
Medline (OVID)	1 exp Anticoagulants/ (217958) 2 "Vitamin K"/ai or "Vitamin K"/tu or VKA.ti,ab. or "vitamin K".ti,ab. (16200) 3 (4-hydroxycoumarin* or warfarin*).ti,ab. (23900) 4 (heparin* or LMWH* or dalteparin* or enoxaparin* or nadroparin* or tinzaparin* or pentasacharide* or aspirin* or 'acetylsalicylic acid').ti,ab. or aspirin/ (151245) 5 (Rivaroxaban* or Dabigatran* or Apixaban* or Edoxaban* or ("New Oral Anticoagulant*" or "Novel Oral Anticoagulant*" or NOAC*)).ti,ab. (10240) 6 ("Direct Oral Anticoagulant*" or DOAC*).ti,ab. (2795) 7 1 or 2 or 3 or 4 or 5 or 6 (325243) 8 exp Hemorrhage/ (323564) 9 (H?emorrhage* or bleed*).ti,ab. (357652) 10 8 or 9 (524846) 11 7 and 10 (47897) 12 limit 11 to (yr="2015 -Current" and (dutch or english)) (12091) 13 (resum* or restart* or recommenc* or reinitiat*).ti,ab. (38999) 14 12 and 13 (278) 15 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (430019) 16 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1942747) 17 14 and 15 (28)

	18 (14 and 16) not 17 (55) 19 14 not (17 or 18) (195) 20 17 or 18 or 19 (278)

Bijlage 1 Schriftelijke knelpuntenanalyse

De deelnemende partijen* zijn gevraagd om hun mening te geven over:

- Het conceptraamwerk zoals dat al in overleg met de voorzitter is opgesteld;
- De geldigheid van de bestaande modules uit de richtlijn Antitrombotisch beleid;

Daarnaast was er de mogelijkheid om nieuwe thema's aan te dragen alsook om een top-3 van modules aan te geven.

In onderstaande uitwerking zijn de reacties van de partijen opgenomen. In dit tabblad is ook de prioritering aangegeven. Belangrijk om hier mee te nemen is dat de partijen een top-3 hebben kunnen aangeven en dat niet alle partijen op deze vraag hebben gereageerd. De groen gearceerde items zijn door tenminste 1 partij geprioriteerd. Tijdens de werkgroepvergadering is aan de hand van onderstaande input besproken welke 10 knelpunten uitgewerkt zullen gaan worden.

*De volgende partijen zijn benaderd voor de schrifteljke knelpuntenanalyse: Nederlandse Internisten Vereniging, Nederlandse Vereniging voor Heelkunde, Nederlandse Vereniging voor Cardiologie, Nederlandse Orthopaedische Vereniging, Nederlandse Vereniging van Maag-Darm-Leverartsen, Nederlandse Vereniging voor Neurologie, Nederlands Huisartsengenootschap, Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde, Nederlandse Vereniging voor Anesthesiologie, Nederlandse Vereniging voor Obstetrie en Gynaecologie, Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose, Nederlandse Vereniging voor Radiologie, Nederlandse Vereniging voor Dermatologie en Venereologie, Nederlandse Vereniging voor Klinische Geriatrie, Nederlandse Vereniging voor Mondziekten, Kaak- en Aangezichtschirurgie, Nederlandse Vereniging van Ziekenhuisapothekers, Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, Harteraad, Patientenfederatie, Nederlandse Vereniging voor Urologie, Nederlandse Vereniging voor Kindergeneeskunde, Vereniging van Revalidatieartsen, Vereniging Klinische Genetica Nederland, Nederlandse Vereniging voor KNO-Heelkunde en Heelkunde van het Hoofd-Halsgebied, Nederlandse Vereniging voor Intensive Care, Nederlandse Vereniging voor Thoraxchirurgie, Federatie van Nederlandse Trombosediensten, Stuurgroep ketenzorg antistolling, Vereniging van specialisten ouderengeneeskunde, Kennisinstituut Mondzorg, Vereniging Innovatieve Geneesmiddelen, Inspectie voor de Gezondheidszorg en Jeugd, Nederlandse Federatie van Universitair Medische Centra, Nederlandse Vereniging van Ziekenhuizen, Samenwerkende Topklinische opleidingsZiekenhuizen, Verpleegkundigen & Verzorgenden Nederland, Nederlandse Vakgroep Physician Assistant (Nederlandse Associatie Physician Assistants), Zelfstandige Klinieken Nederland, Zorgverzekeraars Nederland, Zorginstituut Nederland

Conceptraamwerk - nieuwe thema's		
Thema	**Uitgangsvraag**	**Opmerking stakeholders**

Antitrombotisch beleid bij endoscopie*	Wat zijn de te nemen maatregelen met betrekking tot antitrombotische therapie rondom endoscopische ingrepen?	**NIV:** beleid bij endoscopie is volstrekt helder. Mogelijk zijn er uitdagingen in de uitvoering maar dat is een andere kwestie.
Behandeling longembolie bij hemodynamisch instabiele patiënten**	Wat is de optimale behandeling van patienten met hemodynamisch instabiele longembolie?	
Behandeling longembolie bij *intermediate high risk* patiënten*	Wat is de optimale behandeling van patienten met *intermediate high risk* longembolie?	
Diagnostiek van diepe veneuze trombose van het been*	Wat is het optimale diagnostisch management van klinisch verdachte diepe veneuze trombose van het been?	
Diagnostiek van diepe veneuze trombose van de arm*	Wat is het optimale diagnostisch management van klinisch verdachte diepe veneuze trombose van de arm?	**FNT**: incl. eerste lijn
Diagnostiek van oppervlakkige tromboflebitis**	Wat is het optimale diagnostisch management van klinisch verdachte oppervlakkige tromboflebitis?	**NVIC:** relevantie van deze vraag is beperkt, lage prioriteit
Diagnostiek van longembolie	Wat is het optimale diagnostisch management van klinisch verdachte longembolie?	
(Langdurige) follow-up van diepe veneuze trombose en longembolie **	Hoe zou de follow-up van patienten met een diepe veneuze trombose of een longembolie er uit moeten zien?	

Aanvullende thema's ingebracht door stakeholders		
Thema	**Uitgangsvraag**	**Opmerking stakeholders**
Antitrombotisch beleid na bariatrische chirurgie		
combinatie van antistolling (duale en triple therapie)		**KNMP**: of valt dit buiten de scope van deze richtlijn?
Tromboseprofylaxe bij patienten met maligniteit *		

Hoe wordt omgegaan met genetisch onderzoek bij patiënten met een DVT/embolie, wanneer is genetisch onderzoek geindiceerd? En wordt hier nog onderscheid gemaakt tussen veel voorkomende risicofactoren en uitgebreider genetisch onderzoek naar zeldzamere risicofactoren/monogene oorzaken voor DVT/Longembolie. En welke adviezen worden gegeven aan familieleden met een genetische aanleg, wanneer is familieonderzoek wel noodzakelijk en wanneer niet (bij welke aanleg en in welke situatie)?		
Een knelpunt is de organisatie van zorg rondom patienten die antistollingsmedicatie gebruiken, om o.a. controleafspraken voor patienten te waarborgen: Het Zinnige Zorg-Verbetersignalement Diepe veneuze trombose en longembolie (okt 2021, paragraaf 3.1) laat zien dat veel patienten niet de controleconsulten krijgen zoals deze worden aanbevolen in de LTA 2020. (Dit toont tevens dat een implementatieplan van aanpassingen in een richtlijn zeer belangrijk is.)		
De behandeling van trombosearm		
Welke patient met trombose komt in aanmerking voor dosisreductie van apixaban of rivaroxaban na 6 maanden?		
Behandeling buikvenetrombose		
Tromboprofylaxe met DOAC's bij ambulante patiënten met een maligniteit. Er zijn resultaten RCT's beschikbaar		
Behandeling van veneuze trombo-embolie (VTE) en preventie van recidief VTE bij voldragen neonaten, zuigelingen en peuters, kinderen en adolescenten jonger dan 18 jaar is nu ook mogelijk met enkele DOAC's (zijn hiervoor recent geregistreerd)*		

Alle relevante COVID modules zouden kunnen worden geïncludeerd + inclusief informatie toevoegen wanneer en hoe te switchen van LMWH naar DOAC's na ontslag uit het ziekenhuis bij aanwezigheid VTE/ preventie recidief VTE bij COVID-patiënten		
porta trombose		
inflammatie-geassocieerde trombose*		
trombose profylaxe op IC (dose en type)*		
Sinustrombose		
Antitrombotisch beleid rondom complexe aortapathologie (dus niet de standaard EVAR's)		
Stentplaatsing bij veneuze pathologie		
Het gebruik van antithrombotica bij leverpatienten: zowel farmacokinetisch, indicaties als qua maatregelen voor correctie (levercirrose patienten hebben een geheel ander evenwicht tussen pro- en anticoagulatie)'.		**NVMDL:** Evt. meenemen in overwegingen bij relevante modules?
Antitrombotische beleid rondom een CABG		
Waarom is in module over antifosfolipiden syndroom en antistolling geen aandacht voor evt trombocytenaggregatieremmers bij patiënten met een arteriële trombose en antifosfolipidensyndroom? In het verleden was in veel ziekenhuizen het protocol om bij een eerste arteriële trombose bij het antifosfolipidensyndroom te starten met een trombocytenaggregatieremmer en pas bij recidieven dit te veranderen naar een VKA. Zou dit niet nog steeds een optie zijn?		Hanneke: binnengekomen in autorisatiefase vorige update, vanuit de **NVN**.

"Over rationele combinaties van stollingsmiddelen is in de richtlijn antitrombotisch beleid niets opgenomen. De ESC richtlijnen zijn redelijk up to date en daar zou bijvoorbeeld naar verwezen kunnen worden als het om cardiale indicaties gaat. De vaatchirurgie richtlijnen zijn daarentegen nogal summier en niet uptodate. Meest recente wat ik kan vinden is dit: Medicatie na bypasschirurgie bij PAV - Richtlijn - Richtlijnendatabase<https://richtlijnendatabase.nl/richtlijn/perifeer_arterieel_vaatlijden_pav/medicatie_na_bypasschirurgie_bij_pav.html> Waarin eigenlijk combinatie tar/anticoagulans niet beschreven staat; daarentegen zijn er publicaties geweest waarin middelen gecombineerd worden en waarnaar al dan niet terecht verwezen wordt. Dit leidt in de praktijk vaak tot irrationele combinaties of wellicht niet opgenomen rationele combinaties."		Hanneke: nagekomen via de NVZA

Bestaande modules die update nodig hebben		
Thema	**Uitgangsvraag**	**Opmerking stakeholders**
Tromboseprofylaxe bij electieve rugchirurgie		**NOV:** update nodig
Tromboseprofylaxe niet-chirurgische patiënten		**NVZA**: GAARNE toevoegen: tromboseprofylaxe bij patienten met een maligniteit (klinisch en poliklinische patienten), **NVIC:** herzien, check voor nieuwe studies, **NVVR:** tromboseprofylaxe bij veneuze stents
Tromboseprofylaxe bij chirurgische patiënten		**NVIC:** herzien, check voor nieuwe studies, NVVR: tromboseprofylaxe bij complexe aortapathologie (de " niet simpele" EVAR's)

Tromboseprofylaxe bij een acute beroerte		**NVIC:** herzien, check voor nieuwe studies
Risico veneuze trombo-embolie bij pilgebruik		**VIG**: "Schrijf het levonorgestrel spiraal (Mirena) voor indien hormonale anticonceptie wordt gewenst die het risico op VTE met zekerheid niet verhoogt." hieraan kan de andere levonorgestrel spiraal worden toegevoegd (https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/l/levonorgestrel__iud_)
Behandeling maligniteit geassocieerde trombose*		**NVZA:** nog geldig, preventie toevoegen. Zie opmerking boven) **VIG:** herzien, verwerken CARAVAGGIO study in deze module. Er zijn nieuwe gegevens beschikbaar gekomen over het gebruik van DOAC's bij volwassenen + Behandeling van veneuze trombo-embolie (VTE) en preventie van recidief VTE bij voldragen neonaten, zuigelingen en peuters, kinderen en adolescenten jonger dan 18 jaar is nu ook mogelijk met enkele DOAC's (zijn hiervoor recent geregistreerd). Hieronder valt ook behandeling van maligniteit geassocieerde trombose. **KNMP:** Herzien, updaten. DOAC nu wel bij maligniteiten, **Menno:** Herzien - dit gezien Caravaggio studie die is gepubliceerd na vorige editie van de module

Initiële behandeling Veneuze Trombo-Embolie		**VIG**: herzien, Andexanet is beschikbaar als antidotum, dit kan in de module verwerkt worden Behandeling van veneuze trombo-embolie (VTE) en preventie van recidief VTE bij voldragen neonaten, zuigelingen en peuters, kinderen en adolescenten jonger dan 18 jaar is nu ook mogelijk met enkele DOAC's (zijn hiervoor recent geregistreerd) + "Behandel patiënten met een diep veneuze trombose of longembolie met een onderliggende maligniteit met LMWH." --> Graag DOAC's hieraan toevoegen; zie module behandeling van maligniteit geassocieerde trombose Deel over VTE en maligniteit moet worden geupdate. **KNMP**: Herzien, updaten. Wel bij rivaroxaban/apixaban een antidotum; DOAC nu wel bij maligniteiten **NVIC:** herzien, check voor nieuwe studies
Thuisbehandeling longembolie		**VIG**: Herzien, er zijn nieuwe gegevens beschikbaar om toe te voegen zoals de resultaten van de HoT-PE studie **KNMP:** Herzien, VKA/ DOACs nog niet meegenomen, **Menno:** Herzien - dit gezien HOME-PE publcatie et cetera
Thuisbehandeling bij diep veneuze trombose		**VIG**: Herzien, behandeling van veneuze trombo-embolie (VTE) en preventie van recidief VTE bij voldragen neonaten, zuigelingen en peuters, kinderen en adolescenten jonger dan 18 jaar is nu ook mogelijk met enkele DOAC's (zijn hiervoor recent geregistreerd) **KNMP**: Herzien, literatuur updaten
Behandeling katheter gerelateerde trombose		**VIG**: Behandeling van veneuze trombo-embolie (VTE) en preventie van recidief VTE bij voldragen neonaten, zuigelingen en peuters, kinderen en adolescenten jonger dan 18 jaar is nu ook mogelijk met enkele DOAC's (zijn hiervoor recent geregistreerd). Hieronder

		valt ook behandeling katheter gerelateerde trombose, **NVIC:** check voor nieuwe studies
DOACs bij kunstkleppen		**NVT:** herzien
<3 mnd mitralisklepimplantatie/reconstructie		**VIG**: herzien, studie data bekend met NOAC's zoals de ENAVLE en de RIVER studies. Advies EHRA richtlijn overnemen.
<3 mnd biologische aortaklep implantatie		**VIG**: Herzien, studie data bekend met NOAC's zoals de ENAVLE, ENVISAGE, ATLANTIS en de RIVER studies. Advies EHRA richtlijn overnemen.
Lange termijn behandeling bij hartklepprotheses		**VIG**: Herzien, overweeg het toevoegen van DOAC's bij patiënten met biologische hartklepprothese met tevens een indicatie voor DOAC-gebruik Nieuwe dat bij AF patienten met bioklep (RIVER. ENAVLE, ENVISAGE, ATLANTIS)
Aortaklepvervanging of sluiting mitraalklep		**VIG**: herzien, nieuwe data gepubliceerd uit grote RCT's. ENIVISAGE TAVI studie bij AF patienten die een TAVI hebben ondergaan.
Bloeding/ingreep bij parenterale antistolling		**NVIC:** herzien, check voor nieuwe studies
Herstarten antistollingstherapie na bloeding		**NVIC:** herzien, check voor nieuwe studies, **NVT:** herzien
Effect acenocoumarol en fenprocoumon		**NVKC:** herzien
Effect LMWH, pentasaccharide of heparinoïde		**NVIC:** herzien, check voor nieuwe studies , meer duidelijkheid mbt anti Xa monitoring is gewenst **NVKC:** herzien
Effect ongefractioneerde heparine		**NVIC:** herzien, check voor nieuwe studies , meer duidelijkheid mbt anti Xa monitoring is gewenst **NVKC:** herzien
Effect fondaparinux		**NVKC:** herzien
Effect bivalirudine		**NVKC:** herzien

Effect argatroban		**NVKC:** herzien, **NVIC:** herzien, check voor nieuwe studies
Effect dabigatran		**NVKC:** herzien
Effect rivaroxaban		**NVKC:** herzien, **VIG:** herzien, tabel 3 kan worden aangevuld met gegevens voor het indicatiegebied "Behandeling van veneuze trombo-embolie (VTE) en preventie van recidief VTE bij voldragen neonaten, zuigelingen en peuters, kinderen en adolescenten jonger dan 18 jaar" zoals vermeld in de SmPC-tekst rivaroxaban
Effect apixaban		**NVKC:** herzien
Effect edoxaban		**NVKC**: herzien, **VIG**: herzien, gekalibreerde Fxa test voor edoxaban beschikbaar en vrij verkrijgbaar. Plasma levels van edoxaban bekend en kunnen worden toegevoegd (zie tabel 11 EHRA Practical Guide)
Effect COX-1-remmers (COX-1)		**NVKC:** herzien
Effect P2Y12-remmers (clopidogrel, prasugrel en ticagrelor)		**NVKC:** herzien

Daarnaast hebben partijen diverse algemene feedbackpunten meegegeven. Deze zijn in onderstaande tabel weergegeven.

Feedback	Partij
de knelpunten waarvan wij als klinisch genetici vinden die nog niet (voldoende) geadresseerd worden (tabblad nieuwe modules) zijn nu deels verweven in een aantal modules (bijvoorbeeld wanneer wel/geen antistolling in het kraambed). Echter is voor zeker niet alle patiënten en familieleden helder wanneer genetisch onderzoek wel/niet zinvol is. Als klinisch genetici ontvangen wij regelmatig vragen/verwijzingen met deze vraag. Het is moeilijk om deze vragen te beantwoorden met behulp van de huidige richtlijn en het zou helpen wanneer hier in de modules (of wellicht een aparte submodule) expliciet aandacht aan wordt besteed.	VKGN

In het kader van het Zinnige Zorg project 'Veneuze trombo-embolien' van het Zorginstituut is een kwalitatief onderzoek gedaan oa naar patientenvoorlichting. Hieruit is naar voren gekomen dat zowel artsen als patienten van mening zijn dat de consultkaart Antistollingsmedicatie verbetert zou kunnen worden. Er wordt aangegeven dat de informatie deels verouderd is en dat de consultkaart visueel aantrekkelijker gemaakt kan worden. Zie paragraaf 3.4.2 van bijgevoegd rapport.	ZINL
De RAB heeft een mooi volledig hoofdstuk Periprocedureel Beleid met subhoofdstukken voor TAR, DOAC en VKA. Bij VKA is het overbruggingsbeleid goed uitgelegd. Voor DOAC en TAR is gedetailleerd weergegeven op welke dag weer met de antistolling mag worden begonnen (afhankelijk van bloedings- en tromboserisico). Voor VKA staat dat er niet. Er wordt impliciet naar de Kunst verwezen, maar daar is de informatie niet zo gedetailleerd voor wat betreft bloedingsrisico. De FNT zal deze informatie aanvullend opnemen.	Federatie Nederlandse Trombosediensten
Hartelijk dank voor de uitnodiging. Bijgaand de input van Harteraad. Wij stellen voor om pas aan te geven bij welke modules wij betrokken willen zijn, wanneer besloten is om welke 10 modules het zal gaan. Wel hebben wij onder het tabblad algemene opmerkingen generieke zaken beschreven waarvan wij het belangrijk achten dat hier aandacht aan wordt besteed bij de prioritering en uitwerking van de modules.	Harteraad*)
Bied patiënten begrijpelijke, laagdrempelige informatie. Mondeling door de specialist, maar ook informatie ter voorbereiding op een afspraak en om op een later moment op terug te vallen. Bijvoorbeeld door middel van filmpjes en/of folders.	Harteraad
Samen beslissen rond medicatiekeuzes. Bied informatie bestaande uit wat mensen wel/niet mogen m.b.t. het dagelijks leven, waarom bepaalde medicatie gebruikt moet worden, wanneer medicatie ingenomen moet worden, waarom op een bepaald middel moet worden overgestapt, hoe om te gaan met bijwerkingen en vooral ook welke keuzes patiënten hebben in medicatiekeuze.	Harteraad
Houd rekening met de individuele wensen en behoeften van patiënten. Bespreek mogelijkheden en beslis samen welke behandeling (of geen behandeling) het beste bij de patiënt past.	Harteraad
Bied patiënten één centraal aanspreekpunt bij vragen. Het is belangrijk voor patiënten om een duidelijk aanspreekpunt te hebben. Dit leidt tot minder verwarring en ongerustheid bij de patiënt en geeft patiënten de benodigde informatie om een goed geïnformeerd besluit te nemen over zijn/haar zorg.	Harteraad

Uit de jaarlijkse Harteraad monitor komt structureel naar voren dat patiënten meer aandacht willen voor psychosociale aspecten. Psychosociale problemen hebben een grote impact op de kwaliteit van leven van patiënten. Door meer aandacht te besteden aan psychosociale problemen en hier betere begeleiding voor te organiseren kan de kwaliteit van leven verbeteren.	Harteraad
Man/vrouw verschillen, maar ook etnische achtergrond en leeftijd (de oudere patiënt bijvoorbeeld) zijn belangrijke thema's die standaard meegenomen moeten worden in onderzoek en/of behandeling. Ook dit thema wordt jaarlijks hoog geprioriteerd door patiënten, zo blijkt uit de Harteraad monitor. Hoe wordt met diversiteit omgegaan binnen de richtlijnmodules en waar kan hierop nog een verbeterslag worden gemaakt?	Harteraad
het is niet duidelijk of arteriele thrombi tot de scope van deze richtlijn behoren	NVIC
P 262 Continueren antistolling na acute veneuze tromboembolie Behandel patiënten met een recidief (idiopathisch of uitgelokte) VTE levenslang met antistollingstherapie. Behandel patiënten met een hoog bloedingsrisico en een recidief VTE ten minste gedurende drie maanden met antistollingstherapie. "Bij een eerste VTE episode lijkt het onderscheid tussen een uitgelokte danwel idiopathische VTE van belang te zijn voor de uiteindelijke gewenste antistollingsduur daar het risico op een recidief verschillend is. Patiënten met een idiopathische VTE hebben een hoger risico op een recidief na beëindiging v/d antistolling ten opzichte van patiënten met een VTE waarbij sprake is van een voorbijgaande risicofactor. Risicofactoren die o.a. in de literatuur worden genoemd: idiopathische proximale DVT, obesitas, mannelijk geslacht, IBD etc. Wordt er momenteel in de praktijk reeds gebruik gemaakt van een risicoscore om de antistollingsduur in te stellen bij patiënten waarbij sprake is van een idiopathische VTE? Fahrni J, Husmann M, Gretener SB, Keo HH. Assessing the risk of recurrent venous thromboembolism a practical approach. Vascular Health and Risk Management 2015: 11 451-459" P 517-518 Meten van effect Aspirine/Clopidogrel Routinematig meten van effecten van TAR's is weinig zinvol. Misschien wel interessant om bij HVZ risicopatiënten in de toekomst te kijken in hoeverre bij het doormaken van een infectie uitgekomen wordt met Acetylsalicylzuur of Clopidogrel.. Zou desnoods tijdelijke intensivering van de antiplaatjestherapie of mogelijk tijdelijke antistollingstherapie het cardiovasculaire risico kunnen verlagen?	KNMP

Hartelijk dank voor uw verzoek en excuses voor onze late reactie. Het NHG zal niet deelnemen aan de aan de knelpuntenanalyse van het cluster Antitrombotisch beleid omdat het ons vanwege het grote aantal clusters waar deelname van het NHG voor gevraagd wordt niet lukt om voor al deze clusters knelpunten te inventariseren. De modules opgenomen in het cluster hebben raakpunten met de volgende richtlijnen van het NHG (zie: https://richtlijnen.nhg.org/): • NHG-Standaard Atriumfibrilleren • NHG-Standaard Diep veneuze trombose Voor huisartsen is het beleid zoals in bovenstaande NHG-Standaarden beschreven leidend. We verwachten dus dat de aanbevelingen van de modules die herzien worden alleen de tweedelijn (en dus niet de huisarts betreffen) en aansluiten op het beleid zoals beschreven in bovenstaande NHG-Standaarden. Mochten er knelpunten zijn op het raakvlak van eerste en tweedelijn, dan verzoeken we u met ons contact op te nemen, zodat we daar over in gesprek kunnen gaan.	NHG