Appendices to Guideline Safe Use of Contrast Media Part 3

This part comprises:

- **Iodine-induced hyperthyroidism**
- **Safe use of contrast media during pregnancy and lactation**
- **Safe use of contrast media in patients with rare diseases**
- **Safe time intervals between contrast media administrations**
- **Contrast induced encephalopathy**
- **Hypersensitivity reactions after contrast media administration (extension of part 2)**
- **Analytical interference of contrast media with laboratory tests**
- **Gadolinium deposition (extension of part 2)**

INITIATED BY
Radiological Society of the Netherlands

IN ASSOCIATION WITH

- Netherlands Association of Internal Medicine (NIV)
- The Dutch Association of Neurosurgery (NVvN)
- The Dutch Society of Allergology and Clinical Immunology (NVvAKI)
- The Dutch Society of Cardiology (NVVC)
- The Dutch Society of Clinical Chemistry and Laboratory Medicine (NVKC)
- The Dutch Society of Endocrinology (NVE)
- The Dutch Society of Neurology (NVN)
- The Dutch Society of Obstetrics and Gynaecology (NVOG)
- The Dutch Society of Surgery (NVvH) / The Dutch Society of Vascular Surgery (NVvV)

WITH THE ASSISTANCE OF
Knowledge Institute of Medical Specialists

FINANCED BY
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Colophon

GUIDELINE SAFE USE OF CONTRAST MEDIA - PART 3

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Index

Appendices to module 1 Prevention of Iodine-Induced Hyperthyroidism after Iodine-Based Contrast Media Administration

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Prevention of IIHT	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps

What are prevention strategies for Iodine-Induced Hyperthyroidism (IIHT) in previously specified risk groups:

- Patients with a history of cardiovascular disease and/or more than 65 years old
- Patients with a history of thyroid problems (goitre, hyperthyroidism, hypothyroidism)
- Patients who receive radioactive iodine treatment of the thyroid

Quality assurance indicators

Not applicable.

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3 years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
1st	1-3 years	Not reported	Not reported	Not reported	Not reported	NVvR, NVvAKI	None
2nd	1-3 years	Not reported	Not reported	Not reported	Not reported	NVvR, NVvAKI	None
3rd	1-3 years	Not reported	Not reported	Not reported	Not reported	NVvR, NVvAKI	None

Evidence tables

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Fricke, 2004	Type of study: prospective comparative study Setting and country: Heart and Diabetes Center North Rhine-Westphalia, Bad Oeynhausen, Germany Funding and conflicts of interest: not reported.	Inclusion criteria: Patients admitted to the hospital for coronary angiography with a basal TSH level of less than 0.3 mU/l and normal levels of T3 and free T4 (fT4). Exclusion criteria: *Patients with immunogenic thyroid diseases, verified by the investigation of thyroid autoantibodies, as well as patients with thyroid-specific medication*.	Describe intervention (treatment/procedure/test): *Coronary angiography was carried out with different amounts of iopromid (157±85 ml), containing 370 mg iodine per millilitre.* Previously described patients were treated 2 weeks with 900 mg perchlorate per day, divided into three doses, starting at least 3 hours before coronary angiography. *Depending on the autonomous volume, thiamazole was administered additionally. Twenty milligrams were given for 7 d if the autonomous volume was more than 5 ml and less than 10 ml. If the autonomous volume was greater than 10 ml, CA*	Describe control (treatment/procedure/test): *Coronary angiography was carried out with different amounts of iopromid (157±85 ml), containing 370 mg iodine per millilitre.* Previously described patients with normal thyroid function did not receive prophylactic medication.	Length of follow-up: 14 and 28 days after coronary angiography Loss-to-follow-up: Loss-to-follow-up: Intervention, N (%): 2 Reasons (describe): In one case, coronary angiography was not performed because of high autonomous volume. In another case, contrast agent was given a second time for angioplasty. Control, N (%): 14 Reasons (describe): because of the lack of feedback from the general practitioner. Incomplete outcome data:	Outcome measures and effect size (include 95%CI and p-value if available): 1.1 Iodine-induced hyperthyroidism *Definition IIHT not reported* I: 2/19 (10.5%) C: 0/56 (0%) 2. Iodine induced hypothyroidism Not reported	Authors conclusion: *Scintigraphy of the thyroid gland is suitable for risk stratification of iodine-induced hyperthyroidism in patients with low TSH undergoing CA. Up to a thyroid uptake (TCTU) of 1%, the risk of iodine-induced hyperthyroidism is negligible, and CA can be performed without administration of PDs. The kind, dosage, and duration of prophylactic therapy in case of the TCTU being higher is still a matter calling for further investigation.*

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		N total at baseline: Intervention (prophylactic medication based on results scintigraphy): 19 Control (no prophylactic medication): 56 Important prognostic factors[2]: No prophylactic medication was given based on scintigraphy under the following circumstances: *1) homogenous tracer distribution in the thyroid, TCTU less than 1.5%, and basal TSH ranging from 0.05 to less*	*was performed only in patients with an urgent clinical indication. In those patients, 60 mg thiamazole was given for the first and 20 mg thiamazole for the second week.* *PDs were given according to the autonomous volume, in six patients perchlorate only, and in 13 patients a combined therapy with thiamazole.*		Intervention: not reported Control: not reported		

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		than 0.3; 2) homogenous tracer distribution in the thyroid, TCTU less than 1.0%, and basal TSH less than 0.05; and 3) focal uptake indicating focal autonomy and TCTU less than 1.0%. Group characteristics not described (age, gender) at baseline. *Thyroid volume at baseline* *I: 35.1 ± 16.2 ml* *C: 27.6 ± 15.6 ml* *There was no major difference in the frequency of thyroid nodules or*					

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		changes of echogenicity of the thyroid gland within the two groups.					
Nolte, 1996	Type of study: prospective randomized study Setting and country: Georg-August-Universität, Göttingen, Germany Funding and conflicts of interest: *Partially supported by the Forum Schilddrüse e.V., Hamburg, Germany.* No conflicts of interest reported.	Inclusion criteria: patients from a iodine deficient area in Germany who were admitted to the hospital for coronary angiography and had euthyroid autonomy defined as: *normal FT3 index and normal FT4 index, delta-TSH < 3.5 //U/ml and a 99mTc uptake (TcU) of more than 1.1% (in order to exclude patients with concurrent iodine contamination*	Describe intervention (treatment/procedure/test): *The mean volume of contrast medium was 149ml and ranged from 50 to 410ml.* *Treatment was begun 1 day before angiography and lasted for 14 days* *Group 1 received 20 mg of thiamazole once a day* *Group 2 was treated with 900 mg of sodium perchlorate (300 mg three times a day)*	Describe control (treatment/procedure/test): *The mean volume of contrast medium was 149ml and ranged from 50 to 410ml.* *Group 3 represented the control group and received no special therapy*	Length of follow-up: 30 days Loss-to-follow-up: Intervention: not reported Control: not reported Incomplete outcome data: Intervention: not reported Control: not reported	Outcome measures and effect size (include 95%CI and p-value if available): Iodine-induced hyperthyroidism *Defined as suppressed TSH and increased FT41 and/or FT3I* Group 1: 1/17 Group 2: 1/17 Group 3: 2/17 2. Iodine induced hypothyroidism *Defined as increased TSH and reduced FT4f 30 days after coronary angiography* Group 1: 0 Group 2: 0 Group 3: 0	Authors conclusion: *The present study shows that in patients with euthyroid functional autonomy and increased risk for the development of iodine-induced hyperthyroidism, thiamazole and sodium perchlorate have some protective effect during iodine contamination when given prophylactically. Thirty days after CA the following effects of prophylactic short-term treatment were seen.* *Despite these significant effects, one patient with a small and short-term*

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		for other reasons). Exclusion criteria: *manifest hyperthyroidism, large autonomous adenoma, immunogenic thyroid disease, urine iodine excretion of more than 200iimol/mol creatinine, instable angina pectoris, second disease with a Karnofsky index of less than 50%, patients older than 75 years or younger than 40 years, application of contrast media in the last 6 months*					*elevation of thyroid hormones was observed in each of the treated groups. This implies that both drugs at the applied doses were not able to totally prevent thyrotoxicosis.* *As hyperthyroidism could not be prevented totally by monotherapy with either thionamide or perchlorate, a combination therapy with thionamide and sodium perchlorate in risk patients could be more effective and should be tested in further trials.*

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		and the concomitant use of thyroid hormones, thyrostatic drugs or amiodarone. <u>N total at baseline</u>: Intervention group 1 (Thiamazole): 17 Intervention group 2 (Perchlorate): 17 Control group 3: 17 <u>Important prognostic factors</u>: *There was no significant difference between groups 1, 2 and 3 with regard to age, sex, mean*					

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		volume of contrast media and goitre size. Side effects of thyrostatic drugs were not observed. N.B. Thyroid volume was increased on average (mean 54.4ml, range 16.3-180ml): 25% of patients showed nodulous goitres, 67% had diffuse goitres and 8% showed a normal thyroid gland.					

Risk of bias table

Study reference	Bias due to a non-representative or ill-defined sample of patients?	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?	Bias due to ill-defined or inadequately measured outcome?	Bias due to inadequate adjustment for all important prognostic factors?

Fricke, 2004	Unlikely, patients were well described	Unclear, no differences in follow up between groups, however missing values were not reported	Unclear, the main outcome IIHT was not defined in the article. The exact numbers were not reported for the outcomes free T3 and T4.	Likely, patients were not comparable due to the selection with scintigraphy. The authors did not adjust for prognostic factors.
Nolte, 1996	Unlikely, patients were well described	Unclear, no differences in follow up between groups, however missing values were not reported	Unlikely, the outcome measures were clearly defined.	Unclear, prognostic factors were not described.

Table of excluded studies

Author and year	Reasons for exclusion
Andersen, 2015	Wrong topic: diagnostic value of scintigraphy
Azizi, 2001	Wrong population: a single iodine oil administration for the treatment of goiter in a iodine-deficient area. No contrast media involved
Bal, 2005	Wrong topic: pre-treatment with telepaque (iopanoic acid) before 131I therapy
Basaria, 2005	Wrong design: narrative review about the effect of amiodarone on the thyroid
Bervini, 2020	Wrong comparison: IIHT prevalence after ICM exposure, no comparison between preventive measures
Bogazzi, 2002 "Preparation with iopanoic…"	Wrong topic: treatment of type II amiodarone-induced thyrotoxicosis: preparation with iopanoic acid before thyrotoxicosis
Bogazzi, 2003 "Treatment of type II…"	Wrong topic: treatment of type II amiodarone-induced thyrotoxicosis
Bonelli, 2018	Wrong design: no comparison between preventive measures, preventive measures not reported
Cha, 2019	Wrong topic: hypersensitivity reactions after contrast media
Conen, 2007	Wrong topic: amiodarone-induced thyrotoxicosis treatment
Conn, 1996	Wrong comparison: no preventive measures, wrong outcome: no IIHT
Eskes, 2009	Wrong design: narrative review, wrong topic: amiodarone and thyroid
Esplugas, 2002	Wrong design: narrative review about contrast media used for coronary interventions and adverse reactions
Fassbender, 2001	Wrong comparison: no preventive measures, preventive measures not reported
Fritzsche, 1993	Article (German) in not available in full text anymore, article not found
Gilligan, 2021	Wrong topic: risk on thyroid dysfunction in children under 2 years old hospitalized and receiving an iodinated based contrast medium
Gorkem, 2016	Wrong comparison: no preventive measures, preventive measures not specifically reported
Gurdogan, 2019	Wrong outcome: contrast-induced nephropathy
Hai-Long, 2020	Wrong comparison: no preventive measures, preventive measures not specifically reported
Hintze, 1999	Wrong design: no comparison between preventive measures, preventive measures not reported
Jarvis, 2016	Wrong comparison: no preventive measures, preventive measures not specifically reported
Kornelius, 2015 "Iodinated Contrast Media Increased the Risk…"	Wrong comparison: no preventive measures, preventive measures not specifically reported
Kornelius, 2016 "Iodinated Contrast Media-Induced Thyroid…"	Wrong comparison: patients with goitre compared with patients without goitre and risk on IIHT. No preventive measures described or compared.
Koroscil, 1997	Wrong design: no comparison between preventive measures, preventive measures not reported
Lee, 2014	Wrong design: narrative review
Li, 2021	Wrong outcome: iodine status after oil-based contrast during preconceptionally hysterosalpingography
Ma, 2016	Wrong design: case report (no preventive measures)
Mann, 1994	Wrong outcome: iodine status after endoscopic retrograde cholangiopancreatography
Marraccini, 2013	Wrong design: no comparison between preventive measures
McCormack, 2013	Wrong design: wrong topic: iobitridol usage in diagnostic imaging
Mekaru, 2008	Wrong comparison: no preventive measures, preventive measures not reported
Narayana, 2011	Wrong topic: amiodarone-induced thyrotoxicosis treatment, wrong study design: narrative review
Nygaard, 1998	Wrong design: no comparison between preventive measures
Ozkan, 2013	Wrong comparison: no preventive measures, wrong outcome: no IIHT
Rhee, 2012 "Association between iodinated…"	Wrong design: risk factor analysis for IIHT, no comparison between preventive measures

Rhee, 2013 "Iodinated contrast media exposure…"	Wrong design: no comparison between preventive measures, preventive measures not reported
Röhrl, 2015	Wrong topic: patient centred interviews about informed consent during cardiovascular procedures
Stanbury, 1998	Wrong design: narrative review.
Thomsen, 2006	Wrong design: European guideline on contrast media. / narrative review
Üreyen, 2020	Wrong topic: complex coronary lesions versus non complex coronary lesions
van der Molen, 2004	Wrong design: narrative review as part of European guideline on contrast media.

Literature search strategy

Search strategy
General information

Guideline: Contrast media part 3	
Research question: Prevention of iodine-induced hyperthyroidism (IIHT) after use of iodinated contrast media (ICM)	
Database(s): Medline (OVID), Embase	Date: 01-07-2021
Search from: >1990	Language: English, Dutch
Literature specialist: Linda Niesink	
Additional information: → For this question we searched for the elements contrast agents/ contrast media (in blue), combined with hyperthyroidism (in green). → The key articles of Lee (2015) and Van der Molen (2004) are included in the search results.	
To be used for guideline text: On 01-07-2021 a systematic search was conducted in the databases Embase (embase.com) and Medline (OVID) using relevant keywords for systematic reviews, RCT's and observational studies about (prevention of) hyperthyroidism when using contrast media. The literature search yielded 188 unique references.	

Results

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	13	2	13
RCTs	83	22	90
Observational studies	64	44	85
Total	160	68	188

Search strategy

Database	Search terms		
Embase	*No.*	*Query*	*Results*
	#1	'contrast medium'/exp OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage OR induced OR enhanced OR exposure OR administration OR iodinated OR iodine*)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti OR 'gadolinium-based':ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadavist:ti,ab OR gadodiamide:ti,ab OR	367056

		gadopentetate:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR sonovue:ti,ab OR optison:ti,ab OR lumason:ti,ab OR definity:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR micropaque:ti,ab OR 'e-z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab OR visipaque:ti,ab OR hexabrix:ti,ab OR iomeron:ti,ab OR iopamiro:ti,ab OR omnipaque:ti,ab OR optiray:ti,ab OR ultravist:ti,ab OR xenetix:ti,ab OR iodixanol:ti,ab OR ioxaglate:ti,ab OR iomeprol:ti,ab OR iopamidol:ti,ab OR iosimenol:ti,ab OR iohexol:ti,ab OR ioversol:ti,ab OR iopromide:ti,ab OR iobitridol:ti,ab	
	#2	'hyperthyroidism'/exp OR hyperthyroid*:ti,ab,kw OR hyperthyreoid*:ti,ab,kw OR hyperthyreosis:ti,ab,kw OR 'thyroid gland hyperfunction':ti,ab,kw OR 'thyroid hyperfunction':ti,ab,kw OR 'thyroideal hyperfunction':ti,ab,kw OR thyreotoxicosis:ti,ab,kw OR 'thiamazole'/exp OR 'perchlorate'/exp OR thiamazole:ti,ab,kw OR methimazole:ti,ab,kw OR perchlorate:ti,ab,kw	89224
	#3	#1 AND #2 AND ([english]/lim OR [dutch]/lim) AND [1990-2021]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	655
	#4	'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	714686
	#5	'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	3323143
	#6	'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 'cohort analysis'/de OR cohort*: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)	6109921
	#7	#3 AND #4 - SRs	13
	#8	#3 AND #5 NOT #7 - RCTs	83

	#9 #3 AND #6 NOT (#7 OR #8) – observational studies	64
	#10 #7 OR #8 OR #9	160
Medline (OVID)	1 exp Contrast Media/ or Barium/ or exp Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium-based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol).ti,ab,kf. (232746) 2 exp Hyperthyroidism/ or exp Methimazole/ or exp Perchlorates/ or (hyperthyroid* or hyperthyreoid* or hyperthyreosis or 'thyroid gland hyperfunction' or 'thyroid hyperfunction' or 'thyroideal hyperfunction' or thyreotoxicosis or thiamazole or methimazole or perchlorate*).ti,ab,kf. (61397) 3 1 and 2 (555) 4 limit 3 to ((english or dutch) and yr="1990 -Current") (323) 5 4 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (256) 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.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (480877) 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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2087471) 8 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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] (3656858) 9 5 and 6 (2) – SRs 10 (5 and 7) not 9 (22) - RCTs 11 (5 and 8) not (9 or 10) (44) – observational studies 12 9 or 10 or 11 (68)	

Appendices to module 2 Safe Use of Contrast Media during Pregnancy

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Safe use of CM in pregnancy	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps

What is the safety profile of contrast media during pregnancy (with sub groups for different trimesters) for mother and child? For clear ethical reasons only preclinical data is available.

Quality assurance indicators

Not applicable.

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
1st	1-3 years	None	Not reported	Not reported	Not reported	NVvR, NVOG	None
2nd	1-3 years	None	Not reported	Not reported	Not reported	NVvR, NVOG	None

Evidence tables

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Han, 2011	Type of study: observational retrospective Setting and country: Korea Funding and conflicts of interest: none reported The authors report no conflicts of interest. Th e authors alone are responsible for the content and writing of the paper	Inclusion criteria: women who were inadvertently exposed to barium-contrasted X-ray of the upper gastrointestinal tract (UGT), i.e. barium swallow, in early pregnancy Exclusion criteria: none reported N total at baseline: Intervention: 32 Control: 94	Describe intervention (treatment/procedure/test): Women who were inadvertently exposed to barium-contrasted X-ray of the upper gastrointestinal tract (UGT), i.e. barium swallow, in early pregnancy Between the 18th and 20th weeks ' gestation, patients underwent physical and high-resolution obstetric ultrasound examinations. Th is high-resolution ultrasound examination was intended to assess proper foetal growth and development, especially to rule out gross malformations, as well as to evaluate the proper location and development of the placenta, and follow-up scans were performed if abnormalities were	Describe control (treatment/procedure/test): For each case included in the study, three age- and graviditymatched consenting controls were identified from a large group of pregnant women who were not exposed to any radio-contrast media or any known or potential human teratogen. At birth, all babies were reviewed by a neonatologist who carefully examined the babies in order to rule out any major or minor gross malformation, neurofunctional abnormalities, or any other possible physiological alteration.	Length of follow-up: unclear, at least until birth so 9 months Loss-to-follow-up: Intervention: N (%) = 10/42 (24%) Spontaneous abortions (n = 1); Voluntary terminations (n = 3); Ongoing pregnancies (n = 2); Lost to follow-up (n = 4) Control: N (%) = 32/126 (25%) Spontaneous abortions (n = 7); Voluntary terminations (n = 6); Ongoing pregnancies (n = 8); Lost to follow-up (n = 11)	Outcome measures and effect size (include 95%CI and p-value if available): There were 32 live-born babies in the exposed group and 94 in the controls. Foetal outcomes among inadvertently exposed women were similar to those observed in the control group (Table II); there was one baby (3.1%) born with a major malformation (left ectopic kidney) in the exposed group and three (3.2%) in the control group (p 1.0). Major congenital malformations in the control group included a baby born with left inguinal hernia; a baby	Only patients who had barium exposure in first trimester are included in this study.

		Important prognostic factors[2]: *For example* *age ± SD:* *I: 31.3 ± 3.5* *C: 31.9 ± 4.1* *Medications *number):* *I: 4.1 ± 4.8* *C: 6.2 ± 4.8* Groups comparable at baseline? Yes	suspected. Blood samples were collected for routine haematological and biochemical tests, and for the triple screening (α - fetoprotein, human chorionic gonadotropin and unconjugated oestriol levels). At the next prenatal visit, patients were provided with the results of the blood tests and ultrasound examination and were counselled accordingly. At birth, all babies were reviewed by a neonatologist who carefully examined the babies in order to rule out any major or minor gross malformation, neurofunctional abnormalities, or any other possible physiological alteration.		Incomplete outcome data: see above	born with meningomyeloceles and a baby born with polydactyly on both hands. One baby was born with minor birth defects in the exposed group (nuchal fold thickness), while in the control group there was a case of gum cyst and another baby born with internal rotation of right foot.	
Rajaram, 2012	Type of study: observational retrospective Setting and country: United Kingdom	Inclusion criteria: all pregnant females investigated for suspected pulmonary embolism who	Describe intervention (treatment/procedure/test): pregnant patients with suspected pulmonary embolism who had CTPA, and hence received	Describe control (treatment/procedure/test): pregnant patients with suspected pulmonary embolism who had perfusion imaging only and did not receive contrast	Length of follow-up: unclear, at least several weeks after birth, so 9 months Loss-to-follow-up: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): The average TSH value for group A, exposure to iodinated contrast	

	Funding and conflicts of interest: not reported, unlikely to be present considering subject and type of study	were admitted to study hospitals from April 2004 to April 2009. Exclusion criteria: none reported N total at baseline: Intervention: 73 Control: 42 Important prognostic factors[2]: *For example age (range):* *I: 32 (21-46)* *C: 30 (17-40)* *Gestational age (range):* *I: 28 (12-40)* *C: 29 (7-38)* Groups comparable at baseline? Yes	intravenous iodinated contrast media A maximum dose of 100 ml of nonionic iodinated low-molecular-weight agent containing 300 mg I ml–1 Ultravist 300 (Schering AG, Berlin, Germany) was used as a standard contrast agent.		Incomplete outcome data: Not reported	agent, was 1.1 mIU ml^{-1}. The average TSH value for group B, no exposure to iodinated contrast agent, was 1.07 mIU ml^{-1}. (p=0.67)	

Risk of bias table

Study reference	Bias due to a non-representative or ill-defined sample of patients?	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?	Bias due to ill-defined or inadequately measured outcome?	Bias due to inadequate adjustment for all important prognostic factors?
Han, 2011	Likely; only patients in first trimester included	Unlikely	Unlikely	Unclear; age and gravidity matched controls used for comparison, but no adjustment for confounders in assessment
Rajaram, 2012	Unlikely	Unlikely	Unlikely	Unclear; groups seem comparable, but no adjustment for confounders in assessment

Table of excluded studies

Author and year	Reasons for exclusion
Ahmet, 2009	Wrong patient population: neonates exposed to CM, not pregnant women
Amin, 2017	No control group, patient populations consist out of premature neonates only
Atwell, 2008	No control group (pregnant patients)
Bekiesinska-Figatowska, 2012	Narrative review
Bellin, 2003	Narrative review
Birchard, 2005	No comparison in defined outcome was made between intervention and control group
Bird, 2019	Does not report defined outcome measures.
Bourjelly, 2010	No control group (pregnant patients)
Choi, 2015	No comparison in defined outcome was made between intervention and control group; intervention groups had 2 patients only.
Colleran, 2020	Questionnaire about common clinical practice in lactating patients, does not answer PICO.
Costello, 2016	Narrative review
De Santis, 2007	No control group (pregnant patients)
Gomes, 2015	Narrative review
Herrey, 2019	No control group, dos not report defined outcome measures
Héredia, 2012	No control group, dos not report defined outcome measures
Kochi, 2012	Control group <10 patients (pregnant patients)
Lum, 2020	Narrative review, not focussed on contrast media safety but on MRI safety in pregnant patients
Patenaude, 2014	Narrative review, not focussed on contrast media safety but on MRI safety in pregnant patients
Proenca, 2021	Narrative review
Raymond, 2010	Narrative review
Ray, 2016	Comparison groups consists out of women with no indication for radiological examination.
Scarsbrook, 2006	Narrative review, not focussed on contrast media safety but on venous thrombosis treatment in pregnant patients
Spencer, 2000	No control group (pregnant patients)
Tannus, 2008	Narrative review, not focussed on contrast media safety but on MRI safety in pregnant patients
Thomsen, 2006	Guideline report, not an original article
Van Welie, 2020	Wrong patient group: preconceptional exposure to contrast media
Van Welie, 2021	Systematic review that studies safety of iodinated contrast media in pregnant patients and neonatal thyroid function – no comparative studies are included in the review.
Webb, 2005	Narrative review, also describes lactation
Williams, 2017	Wrong patient population (preterm infants), no control group.

Literature search strategy

Search strategy

General information

Guideline: Contrast media part 3	
Research question: What is the safety profile of contrast media during pregnancy for mother and child?	
Database(s): Embase, Medline	Date: 26-01-2021
Search from: > 2000	Language: English, Dutch
Literature specialist: Linda Niesink	
Additional information: → For this question we searched for the elements contrast agents/ contrast media (in blue), combined with pregnancy (in green) or lactation/breast-feeding (in orange): → The key article of Webb (2005) is included in the search results. The articles of Mathur (2020) en Tremblay (2012) are excluded because of study design.	

To be used for guideline text:
On 26-01-2021 a systematic search was conducted in the databases Embase (embase.com) and Medline (OVID) using relevant keywords for systematic reviews, RCT's and observational studies about the use of contrast media during pregnancy and the lactation period. The literature search yielded 507 unique references.

Results

	Embase	OVID/MEDLINE	Deduplicated
SRs	56	45	66
RCTs	135	90	165
Observational studies	181	225	276
Total	372	360	507

Search strategy

Database	Search terms		
Embase			
	No.	Query	Results
	#11	#8 OR #9 OR #10	372
	#10	#4 AND #7 NOT (#8 OR #9) - Observational studies	181
	#9	#4 AND #6 NOT #8 - RCTs	135
	#8	#4 AND #5 - SRs	56
	#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 'cohort analysis'/de OR cohort*: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)	5842012
	#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	3202960
	#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	699308

		database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
	#4	#1 AND (#2 OR #3) AND ([english]/lim OR [dutch]/lim) AND [2000-2020]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	2820
	#3	'lactation'/exp OR 'breast feeding'/exp OR 'puerperium'/exp OR lactation:ti,ab,kw OR lactating:ti,ab,kw OR 'breast feeding':ti,ab,kw OR puerperium:ti,ab	187830
	#2	'pregnancy'/exp/mj OR pregnant:ti,ab,kw OR pregnancy:ti,ab,kw	705080
	#1	'contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage OR induced OR enhanced OR exposure OR administration OR iodinated OR iodine*)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti OR 'gadolinium-based':ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadavist:ti,ab OR gadodiamide:ti,ab OR gadopentetate:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR sonovue:ti,ab OR optison:ti,ab OR lumason:ti,ab OR definity:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR micropaque:ti,ab OR 'e-z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab OR visipaque:ti,ab OR hexabrix:ti,ab OR iomeron:ti,ab OR iopamiro:ti,ab OR omnipaque:ti,ab OR optiray:ti,ab OR ultravist:ti,ab OR xenetix:ti,ab OR iodixanol:ti,ab OR ioxaglate:ti,ab OR iomeprol:ti,ab OR iopamidol:ti,ab OR iosimenol:ti,ab OR iohexol:ti,ab OR ioversol:ti,ab OR iopromide:ti,ab OR iobitridol:ti,ab	281802
Medline (OVID)	1 exp *Contrast Media/ or Barium/ or exp Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium-based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol).ti,ab,kf. (188721) 2 exp Pregnancy/ or pregnant.ti,ab,kf. or pregnancy.ti,ab,kf. (1019925) 3 exp Lactation/ or exp Breast Feeding/ or (lactation or lactating or 'breast feeding' or puerperium).ti,ab,kf. (110401) 4 2 or 3 (1076220) 5 1 and 4 (2275) 6 limit 5 to ((english or dutch) and yr="2000 -Current") (1384) 7 6 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (962) 8 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. (502787) 9 (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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2084579) 10 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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] (3641005) 11 7 and 8 (45) - SRs 12 (7 and 9) not 8 (90) - RCTs 13 (7 and 10) not (8 or 9) (225) – Observational studies 14 11 or 12 or 13 (360)

Appendices to module 3 Safe Use of Contrast Media during Lactation

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Safe use of CM during lactation	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps
What is the safety profile of contrast media during the lactation period for mother and child? For clear ethical reasons only preclinical data is available.

Quality assurance indicators
Not applicable.

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
1st	1-3 years	None	Not reported	Not reported	Not reported	NVvR, NVOG	None
2nd	1-3 years	None	Not reported	Not reported	Not reported	NVvR, NVOG	None

Evidence tables
Not applicable.

Table of excluded studies
See chapter 2.

Literature search strategy
See chapter 2.

Appendices to module 4.1 Safe Use of Contrast Media in Patients with Multiple Myeloma

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Safe use of CM in	NVvR	2022	2027	5 years	NVvR	New scientific developments

Multiple Myeloma						

Knowledge gaps

There is no convincing evidence that administration of contrast media to patients with multiple myeloma confers an additional risk for PC-AKI irrespective of renal function. Prospective and well-controlled data in patients with various stages of multiple myeloma are needed to further explore this clinically relevant question.

Quality assurance indicators

Not applicable.

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
1st	1-3 years	None	Not reported	Not reported	Not reported	NVvR	None
2nd	1-3 years	Described in module	Not reported	Not reported	Not reported	NVvR	None

Evidence tables

Not applicable

Table of excluded studies

Author and year	Reasons for exclusion
From, 2008	No patients with multiple myeloma
Hillengass, 2014	Background article about patients with monoclonal plasma cell disorders
Lameire, 2005	Narrative review about acute renal failure in cancer patients
McDonald, 2015	Background article: no patients with multiple myeloma but patients with chronic kidney disease
Meschi, 2006	Narrative review about acute contrast medium induced nephropathy
Moos, 2014 "Patients at risk"	No patients with multiple myeloma
Moos, 2014 "Prediction of presence"	Prediction of kidney disease in general population
Mussap, 2014	Narrative review about role of contrast media in renal failure in patients with multiple myeloma
Palmer, 2002	No patients with multiple myeloma
Sakhuja, 2000	Contrast media only described as risk factor for renal involvement in multiple myeloma
Toprak, 2006	No patients with multiple myeloma
Wu, 2016	No patients with multiple myeloma

Literature search strategy

Search strategy

General information

Guideline: Contrast media part 3	
Research question: What is a safe strategy for use of contrast media in multiple myeloma patients?	
Database(s): Medline (OVID), Embase	Date: 17-02-2021

Search from: >2000	Language: English, Dutch
Literature specialist: Linda Niesink	
Additional information: → For this question we searched for the elements contrast agents/ contrast media (in blue), combined with multiple myeloma (in green): → The key article of Stacul (2018), Crowley (2018), Pahade (2011) are included in the search results. The article of McCarthy (1992) is excluded because of publication year. The article of Sprangers (2018) is excluded because they do not mention any contrast media (or synonym).	
To be used for guideline text: On 17-02-2021 a systematic search was conducted in the databases Embase (embase.com) and Medline (OVID) using relevant keywords for systematic reviews, RCT's and observational studies about the use of contrast media in multiple myeloma. The literature search yielded 124 unique references.	

Results

	EMBASE	**OVID/MEDLINE**	**Deduplicated**
SRs	10	3	10
RCTs	43	14	47
Observational studies	51	48	67
Total	104	65	124

Search strategy

Database	**Search terms**		
Embase	No.	Query	Results
	#1	'contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage OR induced OR enhanced OR exposure OR administration OR iodinated OR iodine*)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti OR 'gadolinium-based':ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadavist:ti,ab OR gadodiamide:ti,ab OR gadopentetate:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR sonovue:ti,ab OR optison:ti,ab OR lumason:ti,ab OR definity:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR micropaque:ti,ab OR 'e-z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab OR visipaque:ti,ab OR hexabrix:ti,ab OR iomeron:ti,ab OR iopamiro:ti,ab OR omnipaque:ti,ab OR optiray:ti,ab OR ultravist:ti,ab OR xenetix:ti,ab OR iodixanol:ti,ab OR ioxaglate:ti,ab OR iomeprol:ti,ab OR iopamidol:ti,ab OR iosimenol:ti,ab OR iohexol:ti,ab OR ioversol:ti,ab OR iopromide:ti,ab OR iobitridol:ti,ab	281568

	#2	'multiple myeloma'/exp OR ((kahler NEAR/2 (disease* OR morbus)):ti,ab,kw) OR ((myeloma NEAR/2 (multiplex OR multiple OR 'plasma cell')):ti,ab,kw) OR myelomatosis:ti,ab,kw	91574
	#3	#1 AND #2 AND ([english]/lim OR [dutch]/lim) AND [2000-2020]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	271
	#4	'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	699308
	#5	'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	3202960
	#6	'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 'cohort analysis'/de OR cohort*: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)	5842012
	#7	#3 AND #4 - SRs	10
	#8	#3 AND #5 NOT #7 - RCTs	43
	#9	#3 AND #6 NOT (#7 OR #8) – observational studies	51
	#10	#7 OR #8 OR #9	104
Medline (OVID)	1 exp *Contrast Media/ or Barium/ or exp Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium-based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or		

	omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol).ti,ab,kf. (189258) 2 exp Multiple Myeloma/ or 'multiple myeloma'.ti,ab,kf. or (kahler adj2 (disease* or morbus)).ti,ab,kf. or (myeloma adj2 (multiplex or multiple or 'plasma cell')).ti,ab,kf. or myelomatosis.ti,ab,kf. (54206) 3 1 and 2 (274) 4 limit 3 to ((english or dutch) and yr="2000 -Current") (159) 5 4 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (153) 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.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (480877) 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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2087471) 8 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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] (3656858) 9 5 and 6 (3) – SRs 10 (5 and 7) not 9 (14) - RCTs 11 (5 and 8) not (9 or 10) – observational studies 12 9 or 10 or 11 (65)

Appendices to module 4.2 Safe Use of Contrast Media in Patients with Pheochromocytoma and Paragangliomas

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Safe use of CM in PPGL patients	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps

- Does intra-arterial administration of contrast media to patients with a PPGL result in a clinically relevant change of plasma catecholamine levels?
- If intra-arterial administration of contrast media to patients with PPGL confers a certain risk, can this be avoided by prophylactic treatment?
- If intra-arterial administration of contrast media to patients with PPGL confers a certain risk, will the type of intra-arterial procedure affect this risk? For example, will the risk be the same for percutaneous coronary intervention and angiography of the leg arteries?

Quality assurance indicators

Not applicable.

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
1st	1-3 years	None	Not reported	Not reported	Not reported	NVvR	None
2nd	1-3 years	None	Not reported	Not reported	Not reported	NVvR	None
3rd	1-3 years	None	Not reported	Not reported	Not reported	NVvR	None

Evidence tables

Not applicable

Table of excluded studies

Author and year	Reasons for exclusion
Bessell-Browne, 2007	Does not comply with PICO (case series)
Dudderidge, 2020	Does not comply with PICO (wrong topic)
Hagan, 2004	Does not comply with PICO (narrative review)
Han, 2019	Does not comply with PICO (wrong topic, wrong patient population)
Maurer, 2011	Does not comply with PICO (wrong topic, wrong patient population)

Literature search strategy

Search strategy

General information

Guideline: Contrast media part 3	
Research question: What is a safe strategy for use of contrast media in pheochromocytoma patients?	
Database(s): Medline (OVID), Embase	Date: 22-02-2021
Search from: >2000	Language: English, Dutch
Literature specialist: Linda Niesink	
Additional information: → For this question we searched for the elements contrast agents/ contrast media (in blue), combined with pheochromocytoma (in green): → The key articles of Baid (2009) and Bessel-Browne (2007) are included in the search results. The article of Mukherjee (1997) is excluded because of publication year. The article of Neumann (2019) is excluded because they do not mention any contrast media (or synonym).	
To be used for guideline text: On 22-02-2021 a systematic search was conducted in the databases Embase (embase.com) and Medline (OVID) using relevant keywords for systematic reviews, RCT's and observational studies about the use of contrast media in pheochromocytoma patients. The literature search yielded 125 unique references.	

Results

	EMBASE	OVID/MEDLINE	Deduplicated
SRs	11	8	12
RCTs	24	11	25
Observational studies	69	57	88
Total	104	76	125

Search strategy

Database	Search terms		
Embase	No.	Query	Results
	#1	'contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage OR induced OR enhanced OR exposure OR administration OR iodinated OR iodine*)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti OR 'gadolinium-based':ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadavist:ti,ab OR gadodiamide:ti,ab OR gadopentetate:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR sonovue:ti,ab OR optison:ti,ab OR lumason:ti,ab OR definity:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR micropaque:ti,ab OR	287003

		'e-z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab OR visipaque:ti,ab OR hexabrix:ti,ab OR iomeron:ti,ab OR iopamiro:ti,ab OR omnipaque:ti,ab OR optiray:ti,ab OR ultravist:ti,ab OR xenetix:ti,ab OR iodixanol:ti,ab OR ioxaglate:ti,ab OR iomeprol:ti,ab OR iopamidol:ti,ab OR iosimenol:ti,ab OR iohexol:ti,ab OR ioversol:ti,ab OR iopromide:ti,ab OR iobitridol:ti,ab	
	#2	'pheochromocytoma'/exp OR 'paraganglioma'/exp OR pheochromocytom*:ti,ab,kw OR pheochromoblastom*:ti,ab,kw OR phaeochromocytom*:ti,ab,kw OR phaeochromoblastom*:ti,ab,kw OR pheochromocytos*:ti,ab,kw OR paraganglio*:ti,ab,kw	41640
	#3	#1 AND #2 AND ([english]/lim OR [dutch]/lim) AND [2000-2020]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	384
	#4	'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	699308
	#5	'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	3202960
	#6	'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 'cohort analysis'/de OR cohort*: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)	5842012
	#7	#3 AND #4 - SRs	11
	#8	#3 AND #5 NOT #7 - RCTs	24
	#9	#3 AND #6 NOT (#7 OR #8) – observational studies	69
	#10	#7 OR #8 OR #9	104
Medline (OVID)	1 exp *Contrast Media/ or Barium/ or exp Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium-based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or		

	gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol).ti,ab,kf. (188788) 2 exp Pheochromocytoma/ or exp Paraganglioma/ or (pheochromocytom* or pheochromoblastom* or phaeochromocytom* or phaeochromoblastom* or pheochromocytos* or paraganglio*).ti,ab,kf. (31853) 3 1 and 2 (436) 4 limit 3 to ((english or dutch) and yr="2000 -Current") (224) 5 4 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (203) 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.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (480877) 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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2087471) 8 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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] (3656858) 9 5 and 6 (8) – SRs 10 (5 and 7) not 9 (11) - RCTs 11 (5 and 8) not (9 or 10) (76) – observational studies 12 9 or 10 or 11 (76)

Appendices to module 4.3 Safe Use of Contrast Media in Patients with Myasthenia Gravis

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Safe Use of CM in Myasthenia Gravis	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps

What is role of contrast media in exacerbations of myasthenia gravis (MG)?
What are effective prevention strategies for MG exacerbations?

Quality assurance indicators

Not applicable.

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
1st	1-3 years	None	Not reported	Not reported	Not reported	NVvR	None

Evidence tables

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Somashekar , 2013	Type of study: retrospective cohort Setting and Country*: single large academic health system; January 1, 1995, and December 31, 2011. Michigan, USA Source of funding and conflicts of interest: D.K.S. No relevant conflicts of interest to disclose. M.S.D. No relevant conflicts of	Inclusion criteria: pediatric and adult patients with myasthenia gravis who underwent computed tomography (CT) (regardless of indication or body part) Exclusion criteria: neonatal and/or congenital-type myasthenia gravis and if there was conflicting and/or inadequate documentation confirming the presence or absence of	Describe intervention: Variety of low-osmolality contrast media Contrast medium type: N (%) Unknown: 54 (48) Iopamidol 300: 32 (29) Iopamidol 370: 11 (10) Iopromide 300: 11 (10) Iohexol 300: 4 (4)	Describe control: Unenhanced CT group	Length of follow-up: 45 days after CT Loss-to-follow-up: Intervention: no loss to follow up because of retrospective study design. Incomplete outcome data: Intervention: no incomplete outcome data because of retrospective study design.	Frequency of acute (≤1 day) disease-related symptoms: I: 6.3% [7/112; 95% CI: 0.03- 0.12] C: 0.6% [1/155; 95% CI: 0.0002-0.04]). P = 0.01 Median time to symptom progression: I: 2.5 days C: 14.0 days P = 0.05 Estimated risk of acute symptom deterioration: 5%–6% above baseline (95% CI: 0%-12%). No difference in symptoms between groups at 2–7 days (P =.70) or 8–45 days (P = .99)	primary end point: exacerbation of myasthenia gravis–related symptoms Study limitations: "It was retrospective and there was selection bias between the control group and the experimental group. Some adverse events may not have been captured. we were unable to determine the volume or type of contrast material administered in a large fraction of patients owing to incomplete documentation" Author's conclusion: In conclusion, we demonstrated a significant association between intravenous

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	interest to disclose. R.H.C. Financial activities related to the present article: none to disclose. Financial activities not related to the present article: is a paid consultant for GE Healthcare; received payment for expert testimony from GE Healthcare, LeClair Ryan, and John Hickey; receives royalties from Lippincott, Williams, and Wilkins. Other relationships: none to disclose. J.R.D. Financial	contrast material administration. <u>Important patient characteristics at baseline</u>: No of patients: N=267 I: 112 C:155 Male sex: (%) I: 57 (51) C: 76 (49) Mean age at CT (y): I: 55 (20) C: 58 (21) Groups comparable at baseline: No significant difference between intervention				contrast material dose and type was unknown in a large minority of patients Adverse Events: <u>Symptom exacerbation within 45 days after CT:</u> I: 7/10 C: 0 <u>Symptom exacerbation occurred within 1 day of CT:</u> I: 4/7 C: 0	*Low-osmolality contrast material and acute myasthenia gravis symptom exacerbation, with an incremental frequency that is 5%–6% above the baseline rate observed in similar patients undergoing unenhanced CT. This suggests a need for caution in administering low-osmolality contrast material to patients with myasthenia gravis, and such patients should not place themselves too far from an acute care hospital for a day or two after contrast-enhanced CT in the event that serious symptoms occur.*

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	activities related to the present article: none to disclose. Financial activities not related to the present article: institution has grants/grants pending from GE Healthcare, Bracco Imaging; and Siemens Medical Solutions. Other relationships: none to disclose. J.H.E. Financial activities related to the present article: none to disclose. Financial activities not related to the present article: is a paid consultant for	and control group, except for "Indication for CT"					

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	GE Healthcare; received payment for expert testimony from law firm representing GE Healthcare. Other relationships: none to disclose.						
Rath, 2017	Type of study: retrospective cohort study Setting and country: Department of Neurology of the Medical University of Vienna; between 2005 and 2015 Vienna, Austria Funding and conflicts of interest: Open	Inclusion criteria: typical clinical symptoms in combination with either a positive test for myasthenia gravis-specific autoantibodies [acetylcholine receptor or muscle-specific kinase (MuSK)], a typical decrement ([10%) shown by repetitive	Describe intervention: Low osmolality iodinated contrast agents (ICAs)	Describe control: Unenhanced CT	Length of follow-up: 30 days Loss-to-follow-up: Intervention: no loss to follow up because of retrospective study design. Incomplete outcome data: Intervention: no incomplete outcome data because of retrospective study design.	Primary endpoint: I: 9 (12.3%); 95% CI 5.8-22.1% C: 2 (3.8%); 95% CI 0.5-13.2% P = 0.12 (OR 3.52, 95% CI 0.73–17.0) Subtypes of endpoint: Severe (death or myasthenic crisis): I: 6 (8.2%) (4 myasthenic crisis, 2 deaths) C: 0 P value = 0.04	Primary endpoint: Clinically relevant deterioration of myasthenic symptoms within 30 days of the CT study, defined as clinical worsening by at least one MGFA class. Secondary endpoints: (a) the occurrence of an immediate, acute adverse reaction as documented in the radiological report (b) in the case of reaching the primary

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	access funding provided by Medical University of Vienna. This study received no specific grant from any funding agency. None of the authors has any conflict of interest to disclose.	nerve stimulation or a positive edrophonium chloride test <u>Exclusion criteria</u>: congenital myasthenia gravis, concomitant serious renal disease, and an age of less than 18 years. <u>Important patient characteristics at baseline:</u> <u>No of patients:</u> N=125 I: 73 C:52 <u>Male sex: (%)</u> I: 31 (42.5)				≥1 increase in MGFA class but not myasthenic crisis or death): I: 3 (4.1%) C: 2 (3.8%) P value = 1.00 Time to primary endpoint: I:11.1 days (SD 8.6) C:13 days (SD 1.4) P value = 0.10 only a single patient (1.4%) with an acute, transient probably anaphylactic reaction (dyspnea) occurring immediately after application of the contrast agent.	endpoint the time (in days) to clinical deterioration after ICA administration. <u>Study limitations:</u> *Selection bias for the enhanced and unenhanced CT scans and the relatively low patient numbers. The retrospective nature of this investigation entails the possibility that some adverse events might have been missed in some patients as we had to rely on electronic medical records. To minimize this effect, we only included patients with a sufficient clinical information available*. <u>Author's conclusion:</u> *We conclude that an acute, non-MG-related adverse reaction is a rare event with a risk comparable to other*

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		C: 25 (48.1) <u>Median age (range):</u> I: 62 (79) C: 64 (77) Groups comparable at baseline: No significant difference between intervention and control group, except for "Concomitant acute diseases at CT, indication and region"					*patients. A delayed worsening of myasthenia gravis-related symptoms might occur in approximately 12% of patients after ICA administration. In most cases, this delayed reaction seems to be a purely temporal rather than a causative association. However, given the inevitable uncertainty regarding this analysis, a causative relationship cannot be excluded in all cases, a view which was only recently exemplified by the case report of a patient developing a myasthenic crisis hours after injection of a low-osmolality ICA.*

Risk of bias table

Study reference	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)
Rath, 2017	Unclear – because only patients with available sufficient data were included, this leads to selection bias, since there is often a reason that some patients files are better documented than others	Unlikely	Unlikely: the outcome was clearly defined and measured.	Unlikely: the outcome was compared to a well-defined control group.
Somashekar, 2013	Unlikely: only patients with Myasthenia gravis, with confirmed symptoms, were included.	Unlikely	Unlikely: the outcome was clearly defined and measured.	Unlikely: the outcome was compared to a well-defined control group.

Table of excluded studies

Author and year	Reasons for exclusion
Bonanni, 2015	Does not comply with PICO (wrong study, letter to editor)
Bonanni, 2014	Does not comply with PICO (wrong study, case report)
Bopeththa, 2019	Does not comply with PICO (wrong study, case report)
Kalita, 2014	Does not comply with PICO (wrong study, wrong comparison and outcome)
Khandelwal, 2016	Does not comply with PICO (wrong study, letter to editor)
Khartade, 2020	Does not comply with PICO (wrong study, case report)
Konen, 2002	Does not comply with PICO (wrong study, wrong comparison and outcome)
Mehrizi, 2015	Does not comply with PICO (wrong study, letter to editor)
Mehrizi, 2014	Does not comply with PICO (wrong population (including children), no comparison group)

Literature search strategy

Search strategy

General information

Guideline: Contrast media part 3	
Research question: What is a safe strategy for use of contrast media in myasthenia gravis patients?	
Database(s): Medline (OVID), Embase	Date: 04-03-2021
Search from: >2000	Language: English, Dutch
Literature specialist: Linda Niesink	
Additional information: → For this question we searched for the elements contrast agents/ contrast media (in blue), combined with myasthenia gravis (in green): → The key articles of Somashekar (2013) and Rath (2017) are included in the search results.	
To be used for guideline text: On 04-03-2021 a systematic search was conducted in the databases Embase (embase.com) and Medline (OVID) using relevant keywords for systematic reviews, RCTs, observational studies and other study designs about the use of contrast media in myasthenia gravis patients. The literature search yielded 84 unique references.	

Results

	EMBASE	OVID/MEDLINE	Deduplicated
SRs	1	0	1
RCTs	4	2	4
Observational studies	14	8	14
Other study designs	54	37	65
Total	**73**	**47**	**84**

Search strategy

Database	Search terms		
Embase	No.	Query	Results
	#1	'contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage OR induced OR enhanced OR exposure OR administration OR iodinated OR iodine*)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti OR 'gadolinium-based':ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadavist:ti,ab OR gadodiamide:ti,ab OR gadopentetate:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR sonovue:ti,ab OR optison:ti,ab OR lumason:ti,ab OR definity:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR micropaque:ti,ab OR 'e-z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab OR visipaque:ti,ab OR hexabrix:ti,ab OR iomeron:ti,ab OR iopamiro:ti,ab OR omnipaque:ti,ab OR optiray:ti,ab OR ultravist:ti,ab OR xenetix:ti,ab OR iodixanol:ti,ab OR ioxaglate:ti,ab OR iomeprol:ti,ab OR iopamidol:ti,ab OR iosimenol:ti,ab OR iohexol:ti,ab OR ioversol:ti,ab OR iopromide:ti,ab OR iobitridol:ti,ab	28727
	#2	'myasthenia gravis'/exp OR ((myasthenia NEAR/2 gravis):ti,ab,kw)	27023
	#3	#1 AND #2 AND ([english]/lim OR [dutch]/lim) AND [2000-2021]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	73
	#4	'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	699308
	#5	'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	3202960
	#6	'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	5842012

	'prospective study'/de OR 'cohort analysis'/de OR cohort*: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) #7 #3 AND #4 - SRs 1 #8 #3 AND #5 NOT #7 - RCTs 4 #9 #3 AND #6 NOT (#7 OR #8) – observational studies 14 #10 #7 OR #8 OR #9 19
Medline (OVID)	1 exp *Contrast Media/ or Barium/ or exp Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium-based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol).ti,ab,kf. (188788) 2 exp Myasthenia Gravis/ or (myasthenia adj2 gravis).ti,ab,kf. (19009) 3 1 and 2 (64) 4 limit 3 to ((english or dutch) and yr="2000 -Current") (37) 5 4 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (30) 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.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (505387) 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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2089139) 8 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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] (3654959) 9 5 and 6 (0) – SRs 10 (5 and 7) not 9 (2) - RCTs

	11 (5 and 8) not (9 or 10) (8) – observational studies 12 9 or 10 or 11 (10)

Appendices to module 4.4 Safe Use of Contrast Media in Patients with Systemic Mastocytosis

Validity and maintenance

Module	Responsible authors)	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Safe Use of CM in Mastocytosis	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps

Ideally, the question whether systemic mastocytosis patients require anti-allergic premedication should be answered by means of a double blinded RCT with and without premedication. It is unlikely that such a trial will be funded.

Alternatively, mastocytosis drug allergy specialists could perform drug provocation tests in a safe setting in their entire cohort of mastocytosis patients to assess the risk of anaphylaxis/allergic reactions; after a negative provocation test, use of premedication should be discouraged.

Quality assurance indicators

Not applicable.

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
1st	1-3 years	Described in module	Described in module	Described in module	Described in module	NVvR, NVvAKI	None
2nd	1-3 years	Described in module	Described in module	Described in module	Described in module	NVvR, NVvAKI	None

Evidence tables

Not applicable

Table of excluded studies

Author and year	Reasons for exclusion
Fellinger, 2014	Patients with elevated BST, not about patients with mastocytosis
Hermans, 2017	Narrative review, could be used as background article for justifications
Idée, 2005	Narrative article about allergic reactions with contrast media, not about patients with mastocytosis
Palmiere, 2014	Narrative article about risk factors of anaphylactic shock after contrast media usage, not about patients with mastocytosis
Szebeni, 2004	Narrative article about the role and activation of the complement system

Literature search strategy

Search strategy

General information

Guideline: Contrast media part 3	
Research question: What is a safe strategy for use of contrast media in systemic mastocytosis patients?	
Database(s): Medline (OVID), Embase	Date: 05-03-2021
Search from: >2000	Language: English, Dutch
Literature specialist: Linda Niesink	
Additional information: → For this question we searched for the elements contrast agents/ contrast media (in blue), combined with systemic mastocytosis (in green): → The key articles of Hermans (2017) and Bonadonna (2014) are included in the search results. The articles of Carter (2019), Olson (2018) and Weingarten (2009) are excluded because of studydesign. The article of Bonadonna (2015) and Pardanani (2019) are excuded because they do not mention 'contrast agents/contrast media' (or synonyms).	
To be used for guideline text: On 05-03-2021 a systematic search was conducted in the databases Embase (embase.com) and Medline (OVID) using relevant keywords for systematic reviews, RCT's and observational studies about the use of contrast media in systemic mastocytosis patients. The literature search yielded 21 unique references.	

Results

	EMBASE	**OVID/MEDLINE**	**Deduplicated**
SRs	4	2	4
RCTs	9	4	10
Observational studies	6	8	7
Total	19	14	21

Search strategy

Database	**Search terms**		
Embase	No.	Query	Results
	#1	'contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage OR induced OR enhanced OR exposure OR administration OR iodinated OR iodine*)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti OR 'gadolinium-based':ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadavist:ti,ab OR gadodiamide:ti,ab OR gadopentetate:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR sonovue:ti,ab OR optison:ti,ab OR lumason:ti,ab OR definity:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR micropaque:ti,ab OR 'e-z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab OR visipaque:ti,ab	287881

		OR hexabrix:ti,ab OR iomeron:ti,ab OR iopamiro:ti,ab OR omnipaque:ti,ab OR optiray:ti,ab OR ultravist:ti,ab OR xenetix:ti,ab OR iodixanol:ti,ab OR ioxaglate:ti,ab OR iomeprol:ti,ab OR iopamidol:ti,ab OR iosimenol:ti,ab OR iohexol:ti,ab OR ioversol:ti,ab OR iopromide:ti,ab OR iobitridol:ti,ab	
	#2	'systemic mastocytosis'/exp OR 'mastocytosis'/exp OR mastocytos*:ti,ab,kw OR 'mast cell*':ti,ab,kw	57918
	#3	#1 AND #2 AND ([english]/lim OR [dutch]/lim) AND [2000-2021]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	103
	#4	'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	699308
	#5	'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	3202960
	#6	'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 'cohort analysis'/de OR cohort*: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)	5842012
	#7	#3 AND #4 - SRs	4
	#8	#3 AND #5 NOT #7 - RCTs	9
	#9	#3 AND #6 NOT (#7 OR #8) – observational studies	6
	#10	#7 OR #8 OR #9	19
Medline (OVID)	1 exp *Contrast Media/ or Barium/ or exp Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium-based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or		

	meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol).ti,ab,kf. (189146) 2 exp Mastocytosis, Systemic/ or exp Mastocytosis/ or mastocytos*.ti,ab,kf. or 'mast cell*'.ti,ab,kf. (46193) 3 1 and 2 (248) 4 limit 3 to ((english or dutch) and yr="2000 -Current") (141) 5 4 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (30) 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.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (505387) 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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2089139) 8 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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] (3654959) 9 5 and 6 (2) – SRs 10 (5 and 7) not 9 (4) - RCTs 11 (5 and 8) not (9 or 10) (8) – observational studies 12 9 or 10 or 11 (14)

Appendices to module 5 Multiple Examinations with Contrast Media in Patients with Normal or Reduced Renal Function

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Safe Time intervals	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps

To quantify the effect of several waiting times on diagnostic interference and safety in subsequent examinations with the same or other CM, in relation to the level of renal insufficiency.

Quality assurance indicators

Not applicable.

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
1st	1-3 years	Possible reduction GBCA use	Time of medical specialist in making local hospital protocols	Personal opinons of rquesting physicians in following local hospital protocols	Transfer into local hospital protocols	NVvR and NVvAKI	None
2nd	> 3 years	Not reported	Not reported	Not reported	When possible integrate into European ESUR CMSC protocols which are published in peer-reviewed literature	NVvR and NVvAKI	None

Evidence tables

Not applicable

Table of excluded studies

Not applicable

Literature search strategy

General information

Guideline: Contrast media part 3	
Research question: What is a safe time interval in patients with reduced renal function between two radiological examinations?	
Database(s): Medline (OVID), Embase	Date: 13-04-2021
Search from: >1975	Language: English, Dutch
Literature specialist: Linda Niesink	
Additional information: → For this question we searched for the elements contrast agents/ contrast media (in blue), combined with pharmacokinetics (in green) and time interval (in orange). Some specific (old) contrast media are excluded (in purple).	
To be used for guideline text: On 13-04-2021 a systematic search was conducted in the databases Embase (embase.com) and Medline (OVID) using relevant keywords for systematic reviews, RCT's, observational studies and other study designs about the pharmacokinetics of contrast media in patients with reduced renal function. The literature search yielded 441 unique references.	

Results

	EMBASE	**OVID/MEDLINE**	**Deduplicated**
SRs	3	2	3
RCTs	64	35	71
Observational studies	22	23	29
Other study designs	299	132	338
Total	388	192	441

Search strategy

Database	**Search terms**		
Embase	No.	Query	Results
	#1	'contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage OR induced OR enhanced OR exposure OR administration OR iodinated OR iodine*)):ti) OR 'barium'/exp/mj OR barium:ti OR 'gadolinium'/exp/mj OR gadolinium:ti OR 'microbubble'/exp/mj OR microbubble*:ti OR 'gadolinium-based':ti,ab OR gbca*:ti OR primovist:ti OR eovist:ti OR omniscan:ti OR magnevist:ti OR optimark:ti OR prohance:ti OR multihance:ti OR dotarem:ti OR gadovist:ti OR gadavist:ti OR clariscan:ti OR gadodiamide:ti OR gadopentetate:ti OR gadoversetamide:ti OR gadoteridol:ti OR gadobenate:ti OR gadoterate:ti OR gadobutrol:ti OR 'gadoxetic acid':ti OR 'gadoxetate disodium':ti OR gadopiclenol:ti OR 'gd dtpa':ti OR 'gd hp do3a':ti OR 'gd dtpa bma':ti OR 'gd dota':ti OR 'gd dtpa bmea':ti OR 'gd bopta':ti OR 'gd bt do3a':ti OR 'gd eob dtpa':ti OR sonovue:ti OR optison:ti OR perflutren:ti OR	111091

		hexafluoride:ti OR micropaque:ti OR 'e-z cat':ti OR polibar:ti OR barite:ti OR baritop:ti OR visipaque:ti OR hexabrix:ti OR iomeron:ti OR iopamiro:ti OR omnipaque:ti OR optiray:ti OR ultravist:ti OR xenetix:ti OR iodixanol:ti OR ioxaglate:ti OR iomeprol:ti OR iopamidol:ti OR iosimenol:ti OR iohexol:ti OR ioversol:ti OR iopromide:ti OR iobitridol:ti OR iopentol:ti OR ioxithalamate:ti	
	#2	'pharmacokinetics'/exp/mj OR pharmacokinetic*:ti OR 'biodistribution'/exp/mj OR biodistribution:ti OR washin:ti OR 'wash in':ti OR washout:ti OR 'wash out':ti OR 'urinary excretion'/exp/mj OR (((kidney OR renal) NEAR/3 (excretion OR elimination)):ti) OR 'half life':ti	323271
	#3	'plasma concentration-time curve'/exp OR ((time NEAR/3 (interval OR point* OR curve)):ti,ab,kw) OR hour*:ti,ab,kw OR day*:ti,ab,kw	3858138
	#4	iopanoate:ti OR iodoxamate:ti OR ioglycamate:ti OR ioglycamide:ti OR iodipamide:ti OR iotroxamide:ti OR cholecystography:ti OR cholecystographic:ti OR cholecystopaques:ti OR fluorescein:ti OR fluoresceinated:ti OR sisomicin:ti OR penicillin:ti OR azlocillin:ti OR gentamycin:ti OR tobramycin:ti OR ciprofloxacin:ti OR cefotaxime:ti	46950
	#5	#1 AND #2 AND #3 AND ([english]/lim OR [dutch]/lim) AND [1975-2021]/py NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT #4	388
	#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	699308
	#7	'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	3202960
	#8	'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 'cohort analysis'/de OR cohort*: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)	5842012
	#9	#5 AND #6 - SRs	3
	#10	#5 AND #7 NOT #6 - RCTs	64
	#11	#5 AND #8 NOT (#9 OR #10) – observational studies	22
	#12	#9 OR #10 OR #11	89

	#13 #5 NOT #12 – other study designs 299
Medline (OVID)	1 exp *Contrast Media/ or *Barium/ or exp *Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or barium or gadolinium or microbubble* or 'gadolinium-based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or clariscan or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or gadopiclenol or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol or iopentol or ioxithalamte).ti. (81162) 2 exp *Pharmacokinetics/ or (pharmacokinetic* or biodistribution or washin or 'wash in' or washout or 'wash out' or ((kidney or renal) adj3 (excretion or elimination)) or 'half life').ti. (120566) 3 ((time adj3 (interval or point* or curve)) or (hour* or day*)).ti,ab,kf. (2621752) 4 (iopanoate or iodoxamate or ioglycamate or ioglycamide or iodipamide or iotroxamide or cholecystography or cholecystographic or cholecystopaque* or fluorescein or fluoresceinated or sisomicin or penicillin or azlocillin or gentamycin or tobramycin or ciprofloxacin or cefotaxime).ti. (42942) 5 (1 and 2 and 3) not 4 (201) 6 limit 5 to ((english or dutch) and yr="1975 -Current") (192) 7 6 not (comment/ or editorial/ or letter/) (192) 8 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. (509388) 9 (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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2097343) 10 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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] (3672356) 11 7 and 8 (2) – SRs 12 (7 and 9) not 11 (35) - RCTs 13 (7 and 10) not (11 or 12) (23) – observational studies 14 11 or 12 or 13 (60)

	15 7 not 14 (132) – other study designs

Appendices to module 6 Prevention of Contrast-Induced Encephalopathy

Validity and maintenance

Module	Responsible authors)	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
CIE Prevention	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps

Due to the low incidence comparative studies for preventative treatment strategies are unlikely to be feasible.

Quality assurance indicators

Not applicable.

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
1st	1-3 years	No additional costs are expected.	There are no feasibility and implementation problems expected.	There are no feasibility and implementation problems expected.	There are no feasibility and implementation problems expected.	NVvR, NVN, NVvH	None

Evidence tables

Not applicable

Table of excluded studies

Author and year	Reasons for exclusion
Allison, 2021	Wrong design: description of CIE cases, no preventive strategies mentioned
Chu, 2020	Wrong intervention: risk factor analysis
Dunkley, 2021	Wrong design: description of CIE case, no preventive strategies mentioned
Guimaraens, 2010	Wrong design: description of CIE case, no preventive strategies
Kariyanna, 2020	Wrong design: narrative review about neurotoxicity after coronary angiography
Kocabay, 2014	Wrong design: description of CIE case, no preventive strategies
Lauer, 2021	Wrong population: patients with suspected GBCA accumulation during surgical removal of brain tumour, wrong outcome: seizures, status epilepticus
Mallio, 2020	Wrong design: narrative review about GBCA
Matsubara, 2017	Wrong design: description of CIE cases, no preventive strategies
Messori, 2005	Wrong intervention: bio-electric activity after GBCA administration, wrong outcome: no CIE
Migdady, 2020	Wrong outcome: no CIE, contrast media not mentioned.
Olchowy, 2017	Wrong design: narrative review about GBCA
Patel, 2020	Wrong design: narrative review about GBCA and adverse events
Quintas-Neves, 2020	Wrong design: narrative review about CIN cases, no description of preventive measures
Spina, 2017	Wrong design: narrative review about CIN cases, no description of preventive measures
Yan, 2013	Wrong design: description of CIE case, no preventive strategies
Zevallos, 2020	Wrong design: description of CIE case, no preventive strategies
Zevallos, 2021	Wrong intervention: blood pressure measurement after GBCA administration, wrong outcome: no CIE
Zhang, 2020	High risk of bias: interventions performed in different hospitals, arterial dose might have been different, CIE observation and treatment might have been biased. Second a very small number of participants per group.

Literature search strategy

Search strategy

General information

Guideline: Contrast media part 3	
Research question: What are the strategies for prevention of CIE?	
Database(s): Embase, Medline	Date: 20-07-2021
Search from: > 2001	Language: English, Dutch
Literature specialist: Linda Niesink	
Additional information: → For this question we searched for the elements contrast agents/ contrast media / angiography (in blue), combined with (contrast-induced) encephalopathy (in green). → The key article of Chu (2020) is included in the search results. The article of Hamra (2017) is excluded because of study design (case-report).	
To be used for guideline text: On 20-07-2021 a systematic search was conducted in the databases Embase (embase.com) and Medline (OVID) using relevant keywords for systematic reviews, RCT's and observational studies about the use of contrast media and the prevention of encephalopathy. The literature search yielded 419 unique references.	

Results

	Embase	OVID/MEDLINE	Deduplicated
SRs	41	21	46
RCTs	91	45	101
Observational studies	173	182	272
Total	305	248	419

Search strategy

Database	Search terms		
Embase	No.	Query	Results
	#1	'contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage OR induced OR enhanced OR exposure OR administration OR iodinated OR iodine*)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti OR 'gadolinium-based':ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadavist:ti,ab OR gadodiamide:ti,ab OR gadopentetate:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR sonovue:ti,ab OR optison:ti,ab OR lumason:ti,ab OR definity:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR micropaque:ti,ab OR 'e-z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab OR visipaque:ti,ab OR hexabrix:ti,ab OR iomeron:ti,ab OR iopamiro:ti,ab OR omnipaque:ti,ab OR optiray:ti,ab OR ultravist:ti,ab OR xenetix:ti,ab OR iodixanol:ti,ab OR ioxaglate:ti,ab OR iomeprol:ti,ab OR iopamidol:ti,ab OR iosimenol:ti,ab OR iohexol:ti,ab OR ioversol:ti,ab OR iopromide:ti,ab OR iobitridol:ti,ab OR 'angiography'/exp OR angiogra*:ti,ab,kw OR 'angiogram'/exp	791221
	#2	'neurotoxicity'/exp/mj OR neurotoxi*:ti,ab,kw OR encephalopath*:ti,ab,kw	195191
	#3	#1 AND #2 AND ([english]/lim OR [dutch]/lim) AND [2001-2021]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	1534
	#4	'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)	714686

		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	
	#5	'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	3323143
	#6	'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 'cohort analysis'/de OR cohort*: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)	6109921
	#7	#3 AND #4 - SRs	41
	#8	#3 AND #5 NOT #7 - RCTs	91
	#9	#3 AND #6 NOT (#7 OR #8) – observational studies	173
	#10	#7 OR #8 OR #9	305
Medline (OVID)	1 exp Contrast Media/ or Barium/ or exp Microbubbles/ or exp Angiography/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium-based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol or angiogra*).ti,ab,kf. (553434) 2 exp Neurotoxicity Syndromes/ or (neurotoxi* or encephalopath*).ti,ab,kf. (148307) 3 1 and 2 (2042) 4 limit 3 to ((english or dutch) and yr="2001 -Current") (1214) 5 4 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (961) 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.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (480877) 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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2087471) 8 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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] (3656858) 9 5 and 6 (21) – SRs 10 (5 and 7) not 9 (45) - RCTs 11 (5 and 8) not (9 or 10) (182) – observational studies 12 9 or 10 or 11 (248)

Appendices to module 7.1 In Vitro Tests in Patients with Hypersensitivity Reactions to Contrast Media

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
In vitro tests for HSR	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps

The currently available *in vitro* tests for immediate hypersensitivity reactions (i.e. tryptase measurement and BAT) do not fully differentiate between IgE- and non-IgE-mediated activation. There is a need for better distinction between these reactions, either by optimizing and standardizing thresholds of the currently available tests, or by developing new diagnostic tools that can distinguish between activation via de FcE-receptor or via other receptors. This distinction is clinically relevant as IgE-mediated IHM have a high recurrence risk and re-exposure is contra-indicated, while this usually not the case for non-IgE-mediated reactions.
For nonimmediate hypersensitivity reactions, there are currently no *in vitro* tests available. Particularly for patients with severe NIHM in which *in vivo* testing is contra-indicated or diagnostics cannot be delayed > 6 months, there is an urgent need for *in vitro* diagnostic modalities.

Quality assurance indicators

Not applicable.

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
1st	1-3 years	Not reported	Described in module	Described in module	Described in module	NVvR, NVvAKI	None
2nd	1-3 years	Not reported	Described in module	Described in module	Described in module	NVvR, NVvAKI	None
3rd	1-3 years	Not reported	Described in module	Described in module	Described in module	NVvR, NVvAKI	None

Evidence tables

Not applicable

Table of excluded studies

Author and year	Reasons for exclusion
Cabañas, 2018	Does not comply with PICO (Wrong study type, no comparison, wrong population)
Kolenda, 2018	Does not comply with PICO (wrong study type, editorial)
Meucci, 2020	Does not comply with PICO (Wrong intervention, wrong comparison)
Sodagari, 2017	Does not comply with PICO (wrong study type, no comparison, case series, wrong outcome)

Tang, 2020	Does not comply with PICO (Wrong study type, no comparison)
Torres, 2021	Does not comply with PICO (Wrong study type, guideline paper)
Zhai, 2017	Does not comply with PICO (wrong outcome)

Literature search strategy

Search strategy

General information

Guideline: Contrast media part 3	
Research question: What should be done in patients with a history of hypersensitivity reactions after CM to decrease the risk of developing a repeat hypersensitivity reaction after CM?	
Database(s): Medline (OVID), Embase	Date: 22-04-2021
Search from: >2017	Language: English, Dutch
Literature specialist: Linda Niesink	
Additional information: → For this question we searched for the elements **contrast agents/ contrast media** (in blue), combined with **hypersensitivity** (in green) and **serum/urine test/ skin test/ prophylactic measures** (in orange): → The key articles of Schrijvers (2019), Kwon (2019), Trautmann (2019), Clement (2018), Schrijvers (2018), Lee (2020), Cha (2019), Dona (2020), Meucci (2020) and Torres (2020) are included in the search results. The article of Rosado Ingelmo (2016) and Dewachter (2014) are excluded because of publication year. The article of Brockow (2020) is excluded because the article is still in press and doesn't have an abstract.	
To be used for guideline text: On 22-04-2021 a systematic search was conducted in the databases Embase (embase.com) and Medline (OVID) using relevant keywords for systematic reviews, RCT's, observational studies and other study designs about hypersensitivity reactions after contrast media. Specifically, the value of serum and/or urine tests, either skin tests or prophylactic measures were sought. The literature search yielded 400 unique references.	

Results

	EMBASE	**OVID/MEDLINE**	**Deduplicated**
SRs	24	28	29
RCTs	56	25	61
Observational studies	75	75	91
Other study designs	164	183	219
Total	319	311	**400**

Search strategy

Database	**Zoektermen**	**Totaal**
PubMed 1985 – januari 2018	((("Contrast Media"[Mesh] OR contrast medi* [tiab] OR contrast agent* [tiab] OR contrast material* [tiab] OR contrast dose [tiab] OR contrast doses [tiab] OR contrast dosage [tiab] OR radiocontrast medi* [tiab] OR radiocontrast agent* [tiab] OR radiopaque medi* [tiab] OR radiocontrast dose [tiab] OR radiocontrast doses [tiab] OR radiocontrast dosage [tiab] OR "Barium"[Mesh] OR barium [tiab] OR gadolinium [tiab] OR microbubble* [tiab]) AND ("Drug Hypersensitivity"[Mesh] OR hypersensitiv* [tiab] OR allerg* [tiab] OR anaphyla* [tiab] OR "Exanthema"[Mesh] OR exanthem* [tiab] OR rash [tiab] OR adverse reaction*[tiab] OR	368

	drug reaction* [tiab] OR urticaria* [tiab] OR erythem* [tiab] OR edema [tiab] OR angioedema [tiab] OR bronchospasm* [tiab] OR hypotension [tiab] OR hypertension [tiab] OR cardiac arrest* [tiab] OR respiratory arrest [tiab] OR "Stevens-Johnson Syndrome"[Mesh] OR stevens johnson syndrome [tiab] OR sjs [tiab] OR toxic epidermal necrolys* [tiab] OR "Drug Hypersensitivity Syndrome"[Mesh] OR dress syndrome [tiab] OR iodide mump* [tiab] OR ((late [tiab] OR delayed [tiab] OR nonimmediate [tiab] OR immediate [tiab] OR acute [tiab] OR severe [tiab]) AND (reaction* [tiab]))) AND (serum hypersensitivity test* [tiab] OR "Immunoglobulin E"[Mesh] OR IgE [tiab] OR "Tryptases"[Mesh] OR tryptase* [tiab] OR urinary histamine metabolite* [tiab] OR "Methylhistamines"[Mesh] OR methylhistamine* [tiab] OR methylimidazole acetic acid* [tiab] OR basophil activation test* [tiab])) AND (("english"[Language]) AND ("1985"[Date - Publication] : "3000"[Date - Publication])) = 145	
Embase (Elsevier)	(('contrast medium'/exp OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti) AND ('hypersensitivity'/exp OR hypersensitiv*:ab,ti OR anaphyla*:ab,ti OR allerg*:ab,ti OR 'rash'/exp OR rash:ab,ti OR 'adverse reaction*':ab,ti OR 'drug reaction*':ab,ti OR urticaria*:ab,ti OR erythem*:ab,ti OR exanthem*:ab,ti OR edema:ab,ti OR angioedema:ab,ti OR bronchospasm*:ab,ti OR 'anaphylactic shock':ab,ti OR hypotension:ab,ti OR hypertension:ab,ti OR 'cardiac arrest':ab,ti OR 'respiratory arrest':ab,ti OR 'stevens johnson syndrome'/exp OR 'stevens johnson syndrome':ab,ti OR sjs:ab,ti OR 'toxic epidermal necrolysis'/exp OR 'toxic epidermal necrolys*':ab,ti OR 'dress syndrome'/exp OR 'dress syndrome':ab,ti OR 'iodide mump*':ab,ti OR (((late OR delayed OR nonimmediate OR immediate OR acute OR severe) NEAR/2 reaction*):ab,ti)) AND (‘serum hypersensitivity test*’:ab,ti OR 'immunoglobulin E'/exp OR IgE:ab,ti OR 'tryptase'/exp OR tryptase*:ab,ti OR ‘urinary histamine metabolite*’:ab,ti OR 'methylhistamine'/exp OR methylhistamine*:ab,ti OR ‘methylimidazole acetic acid*’:ab,ti OR 'basophil activation test'/exp OR ‘basophil activation test*’:ab,ti)) AND [english]/lim AND [1985-2018]/py NOT 'conference abstract':it NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) = 334	

Appendices to module 7.2 Diagnostic Value of Skin Testing for Hypersensitivity Reactions to Contrast Media

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Skin tests for HSR	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps

Current literature is hampered by its quality, as study set-ups are limited, study populations vary, and a gold standard is generally lacking. Multicentre, structured, and prospective clinical studies are required to establish the value of skin tests for HSRs. For such studies, the clinical features of HSR need to be clearly described and immediate HSR are preferably confirmed by increased tryptase levels. Skin tests should be performed within 12 months after the HSR occurred and the culprit should be known. Analysis should include the culprit contrast agent and a panel of potential alternatives; these materials should become easily accessible for all practicing allergologists. Availability of affordable diagnostic test kits including various contrast media would greatly facilitate the diagnostic process. Finally, ST findings should be confirmed with re-exposure to (an alternative) contrast agent in real-life or with a DPT.

Quality assurance indicators

Not applicable.

Implementation of recommendations *(see also barriers in Supplement on p. 103)*

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
1st	1-3 years	Not reported	Described in module	Described in module	Described in module	NVvR, NVvAKI	None
2nd	1-3 years	Not reported	Described in module	Described in module	Described in module	NVvR, NVvAKI	None

Evidence tables

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
Meucci, 2020	Type of study: retrospective study Setting and country: Allergology Unit, Italy, from 2015 to 2018 Funding and conflicts of interest: No conflicts of interest. Source of funding not reported.	Inclusion criteria: Patients with previous reaction to ionic contrast media (ICM) Exclusion criteria: not reported N=98 Prevalence: 1%–3% (to nonionic contrast media) Age: median (range): 65.6 (23–90) Sex: N (%) 45 (45.9%) M 53 (54.1%) F	Describe index test: Skin test with undiluted: Iohexol Iopromide Iodixanol Iopamidol Ioversol Cut-off point(s): Positive skin test: the diameter of the initial wheal had increased ≥3mm and was surrounded by erythema after 15 min Immediate (IHR): <1 hour after ICM administration Delayed (DHR): >1 hour after ICM administration Comparator test: Intradermal test (IDT) with diluted (1:10): Iohexol Iopromide Iodixanol Iopamidol Ioversol Cut-off point(s):	Describe reference test: Drug provocation test (DPT): ICM based on results of skin tests and characteristics of index reaction: If mild, recent (<12 mo) reaction with negative skin tests for culprit (when known), DPT was performed with culprit ICM If patients did not agree on repeated exposure or injection, an alternative ICM was chosen Cut-off point(s): Immediate (IHR): <1 hour after ICM administration Delayed (DHR): >1 hour after ICM administration	Time between the index test and reference test: not mentioned For how many participants were no complete outcome data available? N (%) Data on first exposure ICM: n=40, 40.8% Data on antiallergic premedication: n=16, 16.3% Data on latency from last ICM reaction to workup: n=2, 2.0% Reasons for incomplete outcome data described? Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Negative predicted value: skin tests IHR: 96.2% DHR: 58.8% p<.0001 (Fisher's exact test) when administering ICM different than culprit. DPT with culprit ICM: 50%	

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
			Positive test: the diameter of the initial wheal had increased ≥3mm and was surrounded by erythema after 20 min Immediate (IHR): <1 hour after ICM administration Delayed (DHR): >1 hour after ICM administration				

Risk of bias table

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
Meucci, 2020	Was a consecutive or random sample of patients enrolled? Unclear No information on how study participants were included/selected Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? No	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 Not clear if outcome assessors were similar for index and reference tests.	Was there an appropriate interval between index test(s) and reference standard? Unclear Not mentioned in the paper. Did all patients receive a reference standard? Yes Did patients receive the same reference standard? No Patients received same test, but with different contrast media, for provocation. No risk of bias.	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
				Were all patients included in the analysis? No	
	CONCLUSION: Could the selection of patients have introduced bias? Unclear RISK: UNCLEAR	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? No RISK: LOW	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear RISK: UNCLEAR	CONCLUSION Could the patient flow have introduced bias? Yes RISK: HIGH	

Table of excluded studies

Author and year	Reasons for exclusion
Al-Ahmad, 2017 "Pattern of inpatient"	Does not comply with PICO (wrong study type)
Al-Ahmad, 2017 "Successful desensitization"	Does not comply with PICO (wrong study type)
Aykan, 2020	Does not comply with PICO (wrong study type)
Clement, 2018	Does not comply with PICO (wrong study type, wrong comparison)
Harr, 2018	Does not comply with PICO (wrong study type)
Hojreh, 2020	Does not comply with PICO (wrong study type)
Khan, 2020	Does not comply with PICO (wrong study type)
Kwon, 2019	Does not comply with PICO (wrong study type)
Lee. 2020	Does not comply with PICO (wrong population)
Machet, 2019	Does not comply with PICO (wrong study type)
Mankouri, 2021	Does not comply with PICO (wrong study type, no comparison)
Rodriguez-Nava, 2019	Does not comply with PICO (wrong study type)
Sanan, 2019	Does not comply with PICO (wrong study type)
Schrijvers, 2019	Does not comply with PICO (wrong study type, editorial)
Sellaturay, 2018	Does not comply with PICO (wrong study type)
Tang, 2020	Does not comply with PICO (wrong study type, no comparison)
Trautmann, 2019	Does not comply with PICO (wrong study type, wrong outcome)
Uppal, 2018	Does not comply with PICO (wrong study type)

Literature search strategy

See module 7.1 In Vitro Tests in Patients with Hypersensitivity Reactions to Contrast Media

Appendices to module 7.3 Risk Factors for Hypersensitivity Reactions to Contrast Media

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Risk Factors to HSR	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps

Identifying risk factors for severe HSR such as anaphylaxis and SCAR has the highest clinical relevance. However, these HSR are (fortunately) rare.
To reliably identify risk factors for these rare HSR, multicentre large prospective studies are required, with proper definitions of the outcome HSR, that ideally are not solely based on clinical outcomes but supported by other diagnostics such as increased tryptase levels or positive skin tests. These studies should include the different types of both ICM and GBCA.

Quality assurance indicators

Every department should have a local protocol in place detailing the follow-up management of a patient that has had a hypersensitivity reaction after contrast media.

1. Hospital-wide protocols about follow-up management of a patient that has had a hypersensitivity reaction after contrast media	
Operationalization	Is there an overall hospital-wide protocol or process-agreement on the follow-up management of a patient that has had a hypersensitivity reaction after contrast media.
Numerator	Not applicable
Denominator	Not applicable
Type of indicator	Input
In- and exclusion criteria	Inclusion A hospital-wide protocol, on the follow-up management of a patient that has had a hypersensitivity reaction after contrast media
Quality domain	Safety and effectivity
Measuring frequency	Once a year
Report year	2020
Frequency of report	Once a year

Each hospital should register which contrast medium is used at every examination, and in what amount.

2. Registration of type and amount of contrast medium used at every examination with contrast	
Operationalization	Is the type and amount of contrast medium used at every examination with contrast systematically registered in the electronic patient dossier?

Numerator	Not applicable
Denominator	Not applicable
Type of indicator	Input
In- and exclusion criteria	Inclusion Systematic registration of type and amount of contrast medium of every examination with contrast in the electronic patient dossier.
Quality domain	Safety and effectivity
Measuring frequency	Once a year
Report year	2020
Frequency of report	Once a year

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
1st	1-3 years	None	Not reported	Not reported	Not reported	NVvR, NVvAKI	None

Evidence tables

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Estimates of prognostic effect	Comments
Cha, 2019	Type of study: prospective cohort Setting and country: South Korea, Between March 2017 and October 2017 Funding and conflicts of interest: All the authors disclosed no relevant relationships.	Inclusion criteria: All patients who underwent contrast-enhanced CT examinations between March 2017 and October 2017. Exclusion criteria: not reported N= 196081 Mean age ± SD: 59.1± 16.0 years Sex: 53.56 % M /46.44 % F Potential confounders or effect modifiers:	Describe prognostic factor(s) and method of measurement: age, sex, and underlying disease such as diabetes mellitus, heart failure, and hyperthyroidism; previous individual history of ICM usage and ICM-related HSRs; previous individual history of drug allergy, asthma, and other allergic diseases; family history of ICM-related HSRs and allergic diseases, including asthma; name of the administered ICM product; regimen of premedication, if administered; and in instances of HSR occurrence, the symptoms, severity (mild, moderate, and severe), and duration of the HSR, along with details on its management. To assess the risk factors for ICM-related HSRs, a control	Duration or endpoint of follow-up: Not reported For how many participants were no complete outcome data available? Not reported Reasons for incomplete outcome data described? Not reported	(Adjusted) Factor-outcome associations (include SEs or 95%CI and p-value if available): The following factors were associated with increased risk of occurrence and recurrence of ICM related HSRs: • Hyperthyroidism (OR: 4.00, 95% CI: 1.4 to 12.1) • Drug allergy (OR: 5.2, 95% CI: 2.8 to 9.7) • Asthma (OR: 2.3, 95% CI: 1.1 to 4.9) • Other allergic disease (OR: 9.5, 95% CI: 4.1 to 22.1) • Past history of ICM exposure o HSR to ICM (OR: 56.3, 95% CI: 20 to 151) • Family history o HSR to ICM (OR: 11.1, 95% CI: 1.4 to 85.9)	

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Estimates of prognostic effect	Comments
		age, sex, ICM product used, and the institution	group was selected among patients without HSRs, after 1:1 matching for age, sex, ICM product used, and the institution. When the occurrence of HSR was reported, control group was selected on a case-by-case basis from the patients of the same age, sex, and institution with the same ICM product administered within 1-week interval from the HSR occurrence. Comparisons between patients with HSR occurrence during the study period and a control group without HSRs were performed. In addition, patients who experienced recurrent HSRs were compared with those who had previously experienced an HSR but had not shown recurrence, to identify the risk factors for its recurrence (Fig 1).		The following factor were associated with decreased risk of occurrence and recurrence of ICM related HSRs: • Past history of ICM exposure o No HSR to ICM usage (OR: 0.7, 95% CI: 0.6 to 0.8) Incremental predictive value[1]: Not reported	

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Estimates of prognostic effect	Comments
Endrikat, 2020	Type of study: case control Setting and country: Europe, Asia (excluding China), China, Africa Funding and conflicts of interest: Three authors are employees of Bayer; R.K. is a statistician for PAREXEL and paid for his service.	Inclusion criteria: The population were composed of patients who received iopromide 300 or 370 mg I/mL (Ultravist 300/370; Bayer AG, Germany) either IA or IV for contrast-enhanced CT scans for various diagnostic reasons. Exclusion criteria: Patients with unspecific reactions (eg, headache, nausea) and possibly procedure-related reactions (eg, drop in blood pressure, bradycardia, tachycardia) N= 133,331	Describe prognostic factor(s) and method of measurement: The primary target variable was the risk (odds ratio) of having a hypersensitivity reaction after IA versus IV administration of iopromide, adjusted for potential confounders. Secondary target variables pertained to assessing the impact of pretreatment with antihistamines/corticosteroids and to evaluate the profile of reactions within each route of administrations.	Duration or endpoint of follow-up: Not reported For how many participants were no complete outcome data available? N (%):17,763 Reasons for incomplete outcome data described? A total of 17,763 patients had to be excluded from the FAS as key parameters were not sufficiently recorded.	(Adjusted) Factor-outcome associations (include SEs or 95%CI and p-value if available): The following factors were associated with increased risk of HSR: • Age o 50-<65 (OR: 1.67, 95% CI: 1.38 to 2.02) o 18-<50 (OR: 2.16, 95% CI: 1.78 to 2.62) • Female (OR: 1.16, 95% CI: 1.01 to 1.34) • Diabetes mellitus (OR: 1.54, 95% CI: 1.19 to 2.00) • Allergy (OR: 3.61, 95% CI: 2.84 to 4.59) • Asthma (OR: 2.14, 95% CI: 1.26 to 3.62) • Contrast media reaction (OR: 4.31, 95% CI: 2.75 to 6.75) • Other concomitant disease: (OR: 1.42, 95% CI: 1.19 to 1.70)	

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Estimates of prognostic effect	Comments
		Mean age ± SD: 50.9 ± 15.72 Sex: 56.4 % M / 43.6 % F Potential confounders or effect modifiers: geographic region (China, Asia), age, examination region (abdomen, heart, thorax, pelvis, kidneys), indication (tumor), and type of examination (CT, angiocardiography). No difference was seen for premedication, neither for corticosteroids nor for H1/H2 blocker			• Geographic region: Asia (OR: 1.80, 95% CI: 1.54 to 2.11) • Dose of iodine in CM o >20–40 g (OR: 1.24, 95% CI: 1.01 to 1.51) • Iopromide concentration o Iopromide 370 (OR: 1.31, 95% CI: 1.12 to 1.54) The following factor were associated with increased risk of HSR: • IA Injection route (OR: 0.23, 95% CI: 0.16 to 0.32) Incremental predictive value[1]: Not reported	
Kim, 2017	Type of study:	Inclusion criteria: Using the	Describe prognostic factor(s) and method of measurement:	Duration or endpoint of follow-up:	(Adjusted) Factor-outcome associations (include SEs or	

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Estimates of prognostic effect	Comments
	Retrospective cohort Setting and country: South Korea, January 2006 and December 2010 Funding and conflicts of interest: This research was supported by a grant from the Ministry of Food and Drug Safety for the operation of the regional pharmacovigilance centre in 2016.	spontaneous reporting programme and CDRS, 1969 immediate ADRs from 286 087 examinations of 142 099 patients who performed contrasted CT examinations between January 2006 and December2010 were enrolled in this study, and their medical records were reviewed. Exclusion criteria: Not reported N= 142 099 Mean age ± SD: 51.60± 18.50	Possible risk factors for immediate ADR were also examined. Cases involving the following RCMs were considered (Table 1): iobitridol (Guerbet, Sulzbach, Germany), iohexol (GE healthcare, Amersham, UK), iopamidol (Bracco, Milan, Italy), and iopromide (Schering, Berlin, Germany). Cases were grouped according to the frequency of CT examinations per day (single CT, multiple CT). Single CT refers to one CT examination per day, while multiple CT refers to more than one CT examination per day. Patient age, gender, and body weight were also considered.	Not reported For how many participants were no complete outcome data available? N (%): Not reported Reasons for incomplete outcome data described? Not reported	95%CI and p-value if available): The following factors were associated with increased risk of immediate ADR: •Types of RCMs oIohexol (OR: 1.36, 95% CI:1.08 to 1.72) oIopamidol (OR: 1.59, 95% CI: 1.28 to 1.98) oIopromide (OR: 2.72, 95% CI: 2.17 to 3.41) •Multiple CT (OR: 2.13, 95% CI: 1.89 to 2.38) •Female (OR: 1.51, 95% CI: 1.36 to 1.67) •Age 20 to 50 (OR: 1.55, 95% CI: 1.01 to 2.37) •Body weight (OR: 1.02, 95% CI: 1.01 to 1.02) The following factors were associated with increased risk of anaphylaxis: •Iopromide (OR: 6.24, 95% CI: 1.32 to 29.44)	

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Estimates of prognostic effect	Comments
		Sex: 50.6 % M / 49.4 % F Potential confounders or effect modifiers: Age, sex, body weight			•Multiple CT (OR: 3.26, 95% CI: 1.81 to 5.86) The following factors were not independently associated with the risk of anaphylaxis: Iohexol, Iopamidol, sex, age and body weight. Incremental predictive value[1]: Not reported	
Park, 2019	Type of study: Retrospective cohort Setting and country: South Korea Funding and conflicts of interest: All the authors disclosed no relevant relationships. This study was funded by	Inclusion criteria: patients who had undergone abdominal CT with intravenous contrast material enhancement before (August 2016 to January 2017; control period) or after (August 2017 to January 2018; intervention period) the transition to the lower tube	Describe prognostic factor(s) and method of measurement: Not described explicitly, but described in results section (see column Outcomes).	Duration or endpoint of follow-up: Not reported For how many participants were no complete outcome data available? N (%): 683 (1.41%) Reasons for incomplete outcome data described? One examination was performed with iodixanol and was excluded from Analysis. Information on patient weight was missing	(Adjusted) Factor-outcome associations (include SEs or 95%CI and p-value if available): • Female (RR:1.22 (95% CI: 1.04 to 1.43) • History of acute hypersensitivity to iodinated contrast material (RR: 10.4, 95% CI: 4.51 to 24.2) • Contrast material used for study CT o Iomeprol (RR: 4.48, 95% CI: 3.09 to 6.48) • Iodine concentration for study CT	Statistical analysis regarding identifying the risk factor are not clearly described. Study design is also not suitable for determining the risk factors.

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Estimates of prognostic effect	Comments
	Central Medical Service (Seoul, South Korea) and the Korea Health Technology R&D Project, through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, South Korea	voltage, patients at least 18 years of age, and patients who underwent CT on an outpatient basis. Exclusion criteria: Not reported. N= 48438 Mean age ± SD: 59 ±12 years Sex: 64.1% M / 35.9 % F Potential confounders or effect modifiers: age, sex, body weight, history of acute hypersensitivity reactions to iodinated contrast material,		for 682 examinations (1.3%; 347 and 335 examinations from the control and intervention periods, respectively).	o 350 mg I/mL (RR: 4.66, 95% CI: 2.92 to 7.42) o ≥370 mg I/mL (RR: 2.83, 95% CI: 2.13 to 3.77) The following factor were associated with decreased risk of acute HSRs: • Age (RR: 0.98, 95% CI: 0.97 to 0.98) • Premedication for study CT o Antihistamine alone (RR: 0.39, 95% CI: 0.17 to 0.9) o Steroid with or without antihistamine (RR: 0.37, 95% CI: 0.16 to 0.89) • Type of CT examination o Multiphase (RR:0.41, 95% CI: 0.32 to 0.52) Incremental predictive value[1]: Not reported	

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Estimates of prognostic effect	Comments
		use of premedication, contrast material and concentration, and type of CT examination				
Sohn, 2019	Type of study: Prospective observational Setting and country: South Korea, February 2015 to October 2015 Funding and conflicts of interest: The authors state that this work has not received any funding. The authors of this	Inclusion criteria: Patients who underwent CAG. Exclusion criteria: not reported N= 714 Mean age ± SD: 62.9 ± 10.3 Sex: 71% M/29% F Potential confounders or effect modifiers: not reported.	Describe prognostic factor(s) and method of measurement: To determine the presence of immediate HSR after CAG, a nurse observed patients in the recovery room for 1 h; for delayed HSR, four nurses affiliated with the Pharmacovigilance Centre conducted phone interviews at 6- to 12-h and 1-, 3-, 7-, and 14-days post-examination to investigate the occurrence of following reactions: cutaneous (rash, urticaria, erythema, pruritus, or heat sensation), cardiovascular system (chest discomfort or palpitations), respiratory	Duration or endpoint of follow-up: 2 weeks For how many participants were no complete outcome data available? Not reported Reasons for incomplete outcome data described? Not reported	(Adjusted) Factor-outcome associations (include SEs or 95%CI and p-value if available): Previous IA exposure (+) Unadjusted OR (95% CI): 2.51 (1.08–5.86), p –value: 0.028 Adjusted OR (95% CI): 2.92 (1.22–6.96), p –value: 0.015. Iodixanol Unadjusted OR (95% CI): 1.62 (1.07–2.44), p –value: 0.021 Adjusted OR (95% CI): 1.61 (1.07–2.43), p –value: 0.024. Incremental predictive value[1]: Not reported.	

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Estimates of prognostic effect	Comments
	manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.		system (dyspnoea or wheezing), digestive system (nausea or vomiting), nervous system (dizziness), urinary system (urinary symptoms), musculoskeletal system (pain), upper airway system (epistaxis), and fever.			

Risk of bias table

Study reference	Study participation Study sample represents the population of interest on key characteristics?	Study Attrition Loss to follow-up not associated with key characteristics (i.e., the study data adequately represent the sample)?	Prognostic factor measurement Was the PF of interest defined and adequately measured?	Outcome measurement Was the outcome of interest defined and adequately measured?	Study confounding Important potential confounders are appropriately accounted for?	Statistical Analysis and Reporting Statistical analysis appropriate for the design of the study?
Cha, 2019	Low	Low	Low	Low	Low	Low
Endrikat, 2020	Moderate	Low	Low	Moderate	Low	Low
Kim, 2017	Moderate	Low	Low	Low	Moderate	Moderate
Park, 2019	Moderate	Low	Moderate	Low	Low	Low
Sohn, 2019	Low	Low	Moderate	Low	Moderate	Moderate

Table of excluded studies

Author and year	Reason for exclusion
Alamri, 2020	Does not comply with PICO (wrong study type, case report)
An, 2019	Does not comply with PICO (wrong study type, no comparison)
Behzadi, 2018	Does not comply with PICO (wrong comparison set, included old studies which does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only)
Bhatti, 2018	Does not comply with PICO (wrong study type, no comparison)
Böhm, 2018	Does not comply with PICO (wrong study type, case report)
Carter, 2019	Does not comply with PICO (wrong study type)
Colomb, 2018	Does not comply with PICO (wrong study type, case report)
Doña, 2020	Does not comply with PICO (wrong study type, wrong comparison)
Forbes-Amrhein, 2018	Does not comply with PICO (wrong study type, no comparison)
Franckenberg, 2018	Does not comply with PICO (wrong study type, case report)
Inbaraj, 2017	Does not comply with PICO (wrong study type, wrong outcome, no comparison)
Iordache, 2019	
Kim, 2018	Does not comply with PICO (wrong study type, no comparison)
Lee, 2019	Does not comply with PICO (wrong comparison)
Lukawska, 2019	Does not comply with PICO (wrong study type, case report)
Mankouri, 2021	Does not comply with PICO (wrong study type, no comparison, Descriptive study)
Mazori, 2018	Does not comply with PICO (wrong study type, case report)
McDonald, 2019	Does not comply with PICO (wrong comparison, includes pediatric patients)
Morales-Cabeza, 2017	Does not comply with PICO (wrong study type, no comparison)
Moses, 2018	Does not comply with PICO (wrong study type, wrong outcome)
Nadler,2020	Does not comply with PICO (wrong study type, wrong outcome)
Nagai, 2017	Does not comply with PICO (wrong study type, case report)
Nezu, 2020	Does not comply with PICO (wrong study type, case report)
Nucera, 2021	Does not comply with PICO (wrong study type, no comparison)
O'Driscoll, 2019	Does not comply with PICO (wrong study type, case report)
Prieto-Garci-a, 2017	Does not comply with PICO (wrong study type, case report)
Schieda, 2020	Does not comply with PICO (wrong outcome, wrong comparison)
Sessa, 2018	Does not comply with PICO (wrong outcome)
Sodagari, 2018	Does not comply with PICO (wrong study type, wrong outcome, no comparison)
Soria, 2021	Does not comply with PICO (wrong study type, no comparison)
Suh, 2019	Does not comply with PICO (wrong outcome, wrong comparison and including studies with wrong study design)
Tasker, 2019	Does not comply with PICO (wrong study type, review)
Thong, 2020	Does not comply with PICO (wrong study type, review)
Trottier-Tellier, 2018	Does not comply with PICO (wrong study type, wrong outcome, no comparison)
Turner, 2017	Does not comply with PICO (wrong study type, Commentary Review)
Velter, 2017	Does not comply with PICO (wrong study type, case report)
Walker, 2020	Does not comply with PICO (wrong outcome, wrong comparison)
Yang, 2019	Does not comply with PICO (wrong study type, case report)
Yuan, 2021	Does not comply with PICO (wrong study type, in vitro- in vivo study)
Zhai, 2017	Does not comply with PICO (wrong outcome)
Zhang, 2018	Does not comply with PICO (wrong study type, wrong outcome, no comparison)

Literature search strategy

See module 7.1 In Vitro Tests in Patients with Hypersensitivity Reactions to Contrast Media

Appendices to module 7.4 Prophylactic Measures for Prevention of Recurrent Hypersensitivity Reactions to Contrast Media

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Prophylaxis for recurrent HSR	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps

Not reported.

Quality assurance indicators

See previous module.

Implementation of recommendations *(see also barriers in Supplement on p. 103)*

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
All recommendations of module 7.4	1-3 years	Not reported	Described in module	Described in module	Described in module	NVvR, NVvAKI	None

Evidence tables

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Bhatti, 2018	Type of study: retrospective cohort Setting and country: November 1, 2008- January 31, 2016; USA Funding and conflicts of interest: None declared.	Patients with breakthrough reactions to gadobenate dimeglumine Inclusion criteria: Not reported Exclusion criteria: Not reported N total at baseline: Intervention: 19 Control: 97 Important prognostic factors2: Mean age ± SD: I: 51 years (range, 28-90 years) C: Not reported	Describe intervention (treatment/procedure/test): 13-hour premedication: 150 mg prednisone (50mg 13, 7, and 1 hour before contrast material) and 50 mg oral diphenhydramine (1 hour before contrast material)	Describe control (treatment/procedure/test): No premedication	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe)	Outcome measures and effect size (include 95%CI and p-value if available): Breakthrough reactions: I: Mild: 8/19 (42%) Moderate: 9/19 (47%) Severe: 2/19 (11%) C: Mild: 65/97 (67%) Moderate: 27/97 (28%) Severe: 5/97 (5%)	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Sex, female: I: 95% (18/19) C: % Not reported Groups comparable at baseline? Not reported			Not reported		
Cha, 2019	Type of study: Retrospective Multicentre registry Setting and country: seven tertiary referral hospitals in Korea Funding and conflicts of interest: No conflicts of interest	Inclusion criteria: all patients who underwent contrast-enhanced CT examinations between March 2017 and October 2017 and who had experienced an HSR to ICM in the past Exclusion criteria:	Describe intervention (treatment/procedure/test): Mild index reaction, 4 mg of intravenous chlor-pheniramine 30 minutes before ICM administration; Moderate index reaction, 40 mg of intravenous methylprednisolone and 4 mg of intravenous chlorpheniramine 1 hour before ICM administration; Severe index reaction, 40 mg of intravenous methylprednisolone 4 hours and 1 hour before ICM administration and 4 mg of intravenous chlorpheniramine 1 hour	Describe control (treatment/procedure/test): No premedication	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Breakthrough reactions: I: 158/570 (27.7%) C: 19/29 (65.6%) premedication with antihistamine (OR, 0.53; 95% CI: 0.33, 0.86; P = .01)	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Not reported N total at baseline: Total: 570 Intervention: 213/570 (37.4%) Control: Important prognostic factors: Not reported Groups comparable at baseline? Not reported	before ICM administration via the intravenous cannula inserted for ICM injection		Control: N (%) Reasons (describe) Not reported		
Mervak, 2017	Type of study: Retrospective cohort Setting and country: USA Funding and conflicts of interest:	Inclusion criteria: patients who received accelerated 5-hour IV corticosteroid pro-phylaxis before contrast	Describe intervention (treatment/procedure/test): 5-hour IV corticosteroid premedication protocol consisting of 200 mg of IV hydrocortisone administered at 5 hours and 1 hour before CT (total, 400 mg of	Describe control (treatment/procedure/test): 50 mg prednisone administered 13 and 7 hours and 1 hour before CT (total, 150 mg prednisone) and 50 mg diphenhydramine	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported Control:	Outcome measures and effect size (include 95%CI and p-value if available): Breakthrough reaction rate: I: 5% (5/202; 95% CI: 0.8%, 5.7%)	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	No conflict of interest; full report available in the full text article	material–enhanced CT for a prior allergic-like or unknown-type reaction to iodine-based contrast media Exclusion criteria: (a) no contrast-enhanced CT performed within 24 hours (n = 124), (b) receipt of premedication for 10 hours or longer despite initial documentation indicating that an accelerated regimen was planned (n = 21), (b) premedication performed	hydrocortisone administered by means of IV) and 50 mg of IV diphenhydramine administered 1 hour before CT	administered 1 hour before CT	N (%) Reasons (describe) Not reported Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	C: 2.1% (13/626, 95% CI: 1.1%, 3.5%) P = .0181 I: Mild: 2/5 (40%) Moderate: 1/5 (20%) Severe: 2/5 (40%)	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		before an examination other than CT (coronary angiography [n = 17], visceral angiography [n = 11], magnetic resonance im-aging [n = 15], fluoroscopy [n = 3], myelography [n = 1]), (d) subject received oral rather than IV premedication (n = 4), and (e) spurious matching of search terms (n = 1). N total at baseline: Intervention: 202 Control:626					

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Important prognostic factors2: For example age ± SD: I: 58(11-86) C: 57(5-97) Sex: Male I: 81/202 (40%) C: 229/626 (37 %) Groups comparable at baseline? Yes					
Park, 2017	Type of study: Retrospective multicentre cohort Setting and country: 11 centres, Korea 1 January 2014 - 31 December 2014	Inclusion criteria: Patients who had previously experienced a moderate or severe initial HSR to LOCM and in whom the subsequent exposure occurred	Describe intervention (treatment/procedure/test): antihistamines or systemic steroids 0.5–1 hour before re-exposure to LOCM.	Describe control (treatment/procedure/test):	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe)	Outcome measures and effect size (include 95%CI and p-value if available): Recurrence rate of HSR: premedicated with a steroid equivalent to < 40 mg (19.7%; 13/66) or ≥40 mg of prednisolone (26.8%; 15/56) (P = 0.353)	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Funding and conflicts of interest: The authors state that this work has not received any funding. No conflicts of interest.	Exclusion criteria: Not reported N total at baseline: 150 patients, 328 re-exposure Intervention: 240 Control: 88 Important prognostic factors2: age ± SD: 61.7±11.5 I: Not reported C: Not reported Sex: I: % M C: % M Not reported			Not reported Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	steroid premedication: (OR: 1.115, 95% CI: 0.551–2.257; P = 0.762)	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Groups comparable at baseline? Not reported					
Park, 2018	Type of study: Retrospective cohort Setting and country: Korea January 2012 -December 2015 Funding and conflicts of interest: No conflict of interest	Inclusion criteria: patients who experienced mild HSR to ICM before or during the study period and subsequently underwent contrast material–enhanced CT Exclusion criteria: patients premedicated with systemic steroid (n = 363) were excluded N total at baseline:	Describe intervention (treatment/procedure/test): For patients with a mild index reaction, a regimen including 4 mg of intravenous chlorpheniramine 30 minutes before ICM ad-ministration was advised.	Describe control (treatment/procedure/test): No premedication	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	Outcome measures and effect size (include 95%CI and p-value if available): HSR recurrence rate: Premedication with an antihistamine: I: 10.7% C: 16.6% (OR, 0.569; 95% CI: 0.443, 0.731; P, .001) Premedication with the same contrast media: OR, 0.627; 95% CI: 0.430, 0.912; P = .015; with different contrast media: OR, 0.584; 95% CI: 0.4240, 0.776; P, .001	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Intervention: 2388 Control: 1145 *Re-exposures Important prognostic factors2: For example age ± SD: I: C: Not reported Sex: I: % M C: % M Not reported Groups comparable at baseline? Not reported					
Ryoo, 2019	Type of study: Retrospective cohort Setting and country: Korea	Inclusion criteria: patients with mild immediate HSR to GBCA who subsequently underwent	Describe intervention (treatment/procedure/test): intravenous administration of chlorpheniramine 4 mg, 30 minutes before GBCA administration for the patients with	Describe control (treatment/procedure/test): intravenous administration of chlorpheniramine 4 mg, 30 minutes before GBCA administration for the patients with	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported	Outcome measures and effect size (include 95%CI and p-value if available): HSR recurrence rate: Premedication I: 20.4% (61/299)	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	October 2012 - July 2017 Funding and conflicts of interest: The authors report no conflicts of interest.	enhanced magnetic resonance imaging between Exclusion criteria: The patients with unknown culprit agents or unknown adverse reactions were excluded. N total at baseline: 185 patients and 397 re-exposures Intervention: Control: Important prognostic factors2: age ± SD: 51.0 ± 15.2	prior mild HSR, and intravenous administration of methylprednisolone sodium succinate 40 mg plus chlorpheniramine 4 mg, 1 hour before the GBCA administration for the patients with prior moderate or severe HSR.	prior mild HSR, and intravenous administration of methylprednisolone sodium succinate 40 mg plus chlorpheniramine 4 mg, 1 hour before the GBCA administration for the patients with prior moderate or severe HSR.	Control: N (%) Reasons (describe) Not reported Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	C: 17.3% (17/98) OR, 1.221; 95% CI, 0.674–2.211; P = 0.509 antihistamine administration: 19.9%; OR, 1.180; 95% CI, 0.647–2.154; P = 0.589 systemic steroid plus antihistamine: 25.9%; OR, 1.668; 95% CI, 0.609–4.565; P = 0.316	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Sex: 70/185 (37.8%) M Groups comparable at baseline?					
Specjalski, 2020	Type of study: Prospective cohort Setting and country: Poland January 2015-January 2018 Funding and conflicts of interest: Publication of the article financed by ST-554 Gdansk Medical University;	Inclusion criteria: history suggesting a mild hypersensitivity reaction (urticaria, itching, angioedema etc.) Exclusion criteria: Patients with the history of a severe drug hypersensitivity reaction, including	Describe intervention (treatment/procedure/test): 10 mg cetirizine + 20 mg prednisone orally 13, 7 and 1 h before the ICM administration.	Describe control (treatment/procedure/test): 10 mg cetirizine + 50 mg prednisone orally 13, 7 and 1 h before the ICM administration.	Length of follow-up: 24 hours Loss-to-follow-up: Total: 24.8 % (25/101) (9/101 patients consent withdrawal; 14/101 patients alternative test chosen (MRI, USG etc.); 1/101 patient withdrawn due to poor compliance; 11/101 patient withdrawn due to unstable condition)	Outcome measures and effect size (include 95%CI and p-value if available): hypersensitivity reaction: I: 2/40 (5%) C: 4/36 (11.1%) (p = 0.1306)	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	The authors declare no conflict of interest	anaphylaxis as defined by Sampson [5], unstable asthma, renal insufficiency or unstable heart insufficiency were excluded from the study. We also excluded patients with isolated subjective vasomotor symptoms (nausea, sweating, feeling of warmth etc.). N total at baseline: Intervention: 40 Control: 36			Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported		

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Important prognostic factors2: Age (range): I: 48.9 (53–82) C: 46.5 (40-90) Sex: I: 21/40 (52.5%) M C: 15/36 (41.7%) M Groups comparable at baseline? Yes					
Walker, 2020	Type of study: Prospective cohort Setting and country: Canada September 2019-September 2020	Inclusion criteria: Patients with history of immediate HR or “allergy” to GBCA. Exclusion criteria: Patients who received gadoterate	Describe intervention (treatment/procedure/test): 13-hour oral corticosteroid and diphenhydramine premedication	Describe control (treatment/procedure/test): No premedication	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Immediate HRS rate: I: 3.7% (1/27; 95% CI, 0.09%–18.9%) Patients who received adequately dosed corticosteroid	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Funding and conflicts of interest: None declared.	for reasons other than a previous immediate HR, including physiologic reactions, were excluded N total at baseline: 26 patients, 27 injections Intervention: 19/27 Control:8/27 *Injections Important prognostic factors2: age ± SD: 52.1 ± 15.8 Sex: 84.6%(22/26) F Groups comparable at baseline? Yes			Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	premedication: (6.3%; 95% CI, 0.16%–28.7%) Patients who did not receive adequately dosed corticosteroid premedication: (0%, 0/11[upper bound of 95% CI, 25.0%]).	

Risk of bias table

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
Bhatti, 2018	Definitely yes Reason: Participants were selected from same population	Probably no Reason: Although data were collected from department adverse incident forms, It is possible that some reactions occurred	Definitely no Reason: selection criteria were used including participants with the outcome of interest at the start date	Definitely *no* Reason: No matching or adjustment of plausible prognostic variables	*Probably no* Reason: Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables	*Probably no* Reason: Uncertain (no description)	Definitely yes Reason: Follow up was enough.	No information Reason:---	High

		that were not captured on a form.							
Cha, 2019	Definitely yes Reason: Participants were selected from a multicenter registry	Probably yes Reason: questionnaire data with ascertainment rules was used.	Definitely no Reason: selection criteria were used including participants with the outcome of interest at the start date	Definitely yes Reason: Comprehensive matching or adjustment for all plausible prognostic variables	Definitely yes Reason: variables were taken into account in the multivariate analysis.	Probably no Reason: Independent assessment unblinded	Definitely yes Reason: Follow up was enough.	No information Reason: ---	Some concern
Mervak, 2017	Definitely no Reason: Exposed and unexposed presenting to different points of care over a different time frame	Probably yes Reason: Secure record data with ascertainment rules was used.	Definitely no Reason: selection criteria were used including participants with the outcome of interest at the start date	Definitely *no* Reason: No matching or adjustment of plausible prognostic variables	*Probably no* Reason: Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables	*Probably no* Reason: Uncertain (no description)	Definitely yes Reason: Follow up was enough.	No information Reason:---	High
Park, 2018	Definitely yes Reason: Participants were selected from same population	Probably yes Reason: Data collected from Monitoring and Management System with	Definitely no Reason: selection criteria were used including participants with the outcome of	Definitely *no* Reason: No matching or adjustment of plausible prognostic variables	*Probably no* Reason: Prognostic information from data base with no available documentation of quality of	*Definitely no* Reason: Independent assessment unblinded	Definitely yes Reason: Follow up was enough.	No information Reason:---	High

		ascertainment rules was used.	interest at the start date		abstraction of prognostic variables				
Park, 2017	Definitely yes Reason: Participants were selected from same population	Probably no Reason: Uncertain how exposure information obtained	Definitely no Reason: selection criteria were used including participants with the outcome of interest at the start date	Definitely *yes* Reason: Comprehensive matching or adjustment for all plausible prognostic variables	Definitely *yes* Reason: From data base with documentation of accuracy of abstraction of prognostic data	*Probably no* Reason: Uncertain (no description)	Definitely yes Reason: Follow up was enough.	No information Reason:---	High
Specjalski, 2020	Definitely yes Reason: Participants were selected from same population	Probably no Reason: Uncertain how exposure information obtained	Definitely yes Reason: Patients were randomly assigned to one of the premedication arms and were followed for outcome of interest.	Definitely *no* Reason: No matching or adjustment of plausible prognostic variables	*Probably no* Reason: Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables	*Probably no* Reason: Uncertain (no description)	Definitely yes Reason: Follow up was enough.	No information Reason:---	High
Ryoo, 2019	Definitely yes Reason: Exposed and unexposed drawn for same administrative data base of	Probably yes Reason: Data collected from Monitoring and Management System with	Definitely no Reason: selection criteria were used including participants with the outcome of	Definitely *no* Reason: No matching or adjustment of plausible prognostic variables	*Probably no* Reason: Prognostic information from data base with no available documentation of	*Probably no* Reason: Uncertain (no description)	Definitely yes Reason: Follow up was enough.	No information Reason:---	High

	patients presenting at same points of care over the same time frame	ascertainment rules was used.	interest at the start date		quality of abstraction of prognostic variables				
Walker, 2020	Definitely no Reason: Exposed and unexposed presenting to different points of care over a different time frame	Probably yes Reason: questionnaire data with ascertainment rules was used.	Definitely yes Reason: Patients were prospectively idetified and were followd for outcome of interest.	Definitely *no* Reason: No matching or adjustment of plausible prognostic variables	*Probably no* Reason: Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables	*Probably no* Reason: Uncertain (no description)	Definitely yes Reason: Follow up was enough.	No information Reason:---	High

Table of excluded studies

Author and year	Reason for exclusion
Amr, 2020	Does not comply with PICO (wrong comparison)
Ananthakrishnan, 2021	Does not comply with PICO (wrong comparison)
Aykan, 2020	Does not comply with PICO (wrong study type, no comparison)
Benson, 2017	Does not comply with PICO (wrong outcome)
Boehm, 2018	Does not comply with PICO (wrong study type, case report)
Davenport, 2017	Does not comply with PICO (wrong outcome, narrative review)
Jha, 2021	Does not comply with PICO (wrong comparison: PCIs with a prior severe reaction were compared to PCIs with a prior mild-moderate reaction)
Kim, 2018	Does not comply with PICO (No comparison, included children)
Lee, 2017	Does not comply with PICO (wrong comparison, no control group)
Malone, 2020	Does not comply with PICO (wrong study type, case report)
Mizuta, 2020	Does not comply with PICO (wrong study type, case report)
Pugh, 2019	Does not comply with PICO (wrong study type, case report)
Sohn, 2021	Does not comply with PICO (wrong comparison)
Walker, 2020	Does not comply with PICO (most included studies were case reports or case series)

Literature search strategy

See module 7.1 In Vitro Tests in Patients with Hypersensitivity Reactions to Contrast Media

Supplement: Barriers to Implementation – Modules 7.2 and 7.4

As a result of discussion with the Quality Assurance staff of the Radiological Society of The Netherlands the following barriers to implementation of the recommendation in module 7.1-7.4 have been indicated:

1. *Capacity of drug allergy specialist for timely performance of skin tests in patients with hypersensitivity reactions to contrast media*

There is a need for a "Fast Track" analysis in contrast media skin testing, as was already indicated by the GDG during the authorization of the guideline Safe Use of Contrast Media Part 2 in 2019. In daily practice, due to the limited number of drug allergy specialists, the timely performance of skin testing proves to be problematic, especially in those hospitals that have no drug allergy specialists or skin testing facilities.

During a meeting with representatives of the Dutch Society of Allergology and Clinical Immunology this need has again been stressed. Especially oncology patients that are treated with chemotherapy receive repeated CT and/or MR imaging within short time intervals. For these patients a rapid result of skin tests is needed.

The Board of the Dutch Society of Allergology and Clinical Immunology has agreed to work on this, and for the meantime they point to the possibility of using already available time slots for fast diagnosis in the outpatient clinics of its members.

2. *Limited possibilities in current electronic patient record software (Chipsoft/EPIC) for accurate registration of hypersensitivity reactions to contrast media*

In daily practice, the quality of registrations of hypersensitivity reactions to contrast media leaves much to be desired. This is due to the fact that all physicians have rights for registration, even those physicians with little or no experience in working with contrast media. This leads to incomplete or faulty registrations, leading to unnecessary administration of premedication or unnecessarily denying patients good quality medical imaging.

Patients that are referred between hospitals for parts of their treatment constitute a considerable part of this problem. Often these referrals are accompanied by incomplete or faulty registration in one hospital that are taken over by the other hospital due to time constraints.

As already indicated by the GDG during the authorization of the guideline Safe Use of Contrast Media part 2, there is a (growing) need for discussion between representatives of the Board of the Radiological Society of The Netherlands, the Board of the Dutch Society of Allergology and Clinical Immunology, and representatives of the electronic patient record software companies Chipsoft and EPIC (as well as the NICTIZ organization).

Despite long-lasting efforts by Board members of the Dutch Society of Allergology and Clinical Immunology in a Chipsoft Working Group and discussions with the NICTIZ organization, no nationwide usable specific module for accurate and detailed registration of hypersensitivity reactions to contrast media is available, and tools for an accurate exchange of such registrations between hospitals are lacking.

Appendices to module 8 Analytical Interference of Contrast Media with Clinical Laboratory Tests

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Analytical Interference of CM	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps

Selection of literature is performed based on current laboratory practice in the Netherlands. Therefore, obsolete or non-common clinical laboratory tests, are not included.

Quality assurance indicators

Not applicable

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
1st	1-3 years	Not reported	Not reported	Not reported	Not reported	NVvR, NVVC	None
2nd	1-3 years	Not reported	Not reported	Not reported	Not reported	NVvR, NVVC	None
3rd	1-3 years	Not reported	Not reported	Not reported	Not reported	NVvR, NVVC	None

Evidence tables

Not applicable

Table of excluded studies

Not applicable

Literature search strategy

Not applicable

Appendices to module 9.1 Gadolinium Deposition in the Brain and Body

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Gadolinium deposition	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps
Not reported.

Quality assurance indicators
Not applicable.

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
1st	1-3 years	None	Not reported	Not reported	Not reported	NVvR	None
2nd	1-3 years	None	Not reported	Not reported	Not reported	NVvR	None
3rd	1-3 years	None	Not reported	Not reported	Not reported	NVvR	None

Evidence tables
Not applicable

Table of excluded studies
Not applicable

Literature search strategy
Not applicable

Appendices to module 9.2 Strategies for Dose Reduction of Gadolinium-Based Contrast Agents

Validity and maintenance

Module	Responsible authors	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity	Who surveys the actuality of this guideline	Relevant factors for changing recommendations
Reducing GBCA dose	NVvR	2022	2027	5 years	NVvR	New scientific developments

Knowledge gaps
Not reported.

Quality assurance indicators
Not applicable.

Implementation of recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions	Other remarks
All recommendations of module 9.2	1-3 years	Reduction	Described in module	Described in module	Described in module	NVvR	None

Evidence tables
Not applicable

Table of excluded studies
Not applicable

Literature search strategy
Not applicable