Appendices
Guideline
Safe Use of
Contrast Media
- Part 1

Appendices to Chapter 4

Evidence tables

Exclusion after examination of full text (initial search): Risk factors for PC-AKI

Author and year	Reasons to exclude
Abe, 2011	Does not meet selection criteria
Abujudeh, 2008	Examines risk of PC-AKI in patients who underwent 2 CT-scans within 24 hours, not applicable for overall recommendations
Acosta, 2010	Does not meet selection criteria
Agrawal, 2009	Does not meet selection criteria
Aguiar-Suato, 2010	Does not meet selection criteria
Ahuja, 2010	Does not meet selection criteria
Akgullu, 2015	Does not meet selection criteria
Akrawinthawong, 2015	Does not meet selection criteria
Alharazy, 2013	Does not meet selection criteria
Bachorzewska-Gajewska, 2006	Does not meet selection criteria
Balemans, 2012	Does not meet selection criteria
Band, 2007	Does not meet selection criteria
Barbieri, 2014	Does not meet selection criteria
Becker, 2006	Does not meet selection criteria
Canyigit, 2013	Does not meet selection criteria
Caruso, 2011	Does not meet selection criteria
Cely, 2012	Does not meet selection criteria
Chang, 2013	Studies gene polymorphisms and their relation to PC-AKI risk; not applicable in common Dutch clinical practice.
Chavakula, 2013	Does not meet selection criteria
Chen, 2014	Does not meet selection criteria
Cho, 2011	Does not meet selection criteria
Chong, 2009	Does not meet selection criteria
Chong, 2010_1	Does not meet selection criteria
Chong, 2010_2	Does not meet selection criteria
Chong, 2012	Does not meet selection criteria
Cheruvu, 2007	Does not meet selection criteria
Crit, 2006	Does not meet selection criteria
Clark, 2011	Does not meet selection criteria
Clec'h, 2013	Does not meet selection criteria
Colling, 2014	Does not meet selection criteria
Conen, 2006	Does not meet selection criteria
Cowburn, 2005	Does not meet selection criteria
Dangas, 2005	Does not meet selection criteria
Davidson, 2008	Does not meet selection criteria
Ding, 2013	Does not meet selection criteria
Diogo, 2010	Does not meet selection criteria
Diogo, 2014	Does not meet selection criteria
Dittrich, 2006	Does not meet selection criteria
Dittrich, 2007	Does not meet selection criteria
Durukan, 2012	Does not meet selection criteria
Elias, 2005	Does not meet selection criteria
Erdogan, 2003	Does not meet selection criteria
Erselcan, 2012	Does not meet selection criteria
Friedewald, 2013	Does not meet selection criteria
From, 2008	Does not meet selection criteria
Fu, 2013	Does not meet selection criteria
Gao, 2011	Does not meet selection criteria
Gao, 2014	Does not meet selection criteria
Garcia, 2014	Does not meet selection criteria
Garcia-Ruiz, 2003	Does not show multivariate model that predicts risk factors of PC-AKI
Goldenberg, 2005	Does not meet selection criteria

Golshahi, 2014	Does not meet selection criteria
Goo, 2014	Does not meet selection criteria
Guevara, 2004	Does not meet selection criteria
Gurm, 2011	Does not meet selection criteria
Grum, 2013	Does not meet selection criteria
Hassen, 2014	Does not meet selection criteria
Haveman, 2006	Does not meet selection criteria
Hayakawa, 2014	Patient population: patients with hepatocellular carcinoma undergoing trans-arterial chemo-embolization. Article too specific to draw overall conclusions over intra-arterial contrast administration and risk of PC-AKI.
Hernández, 2009	Already included in systematic review Bondi-Zoccai, 2014
Hipp, 2008	Does not meet selection criteria
Holscher, 2008	Does not meet selection criteria
Hoste, 2011	Does not meet selection criteria
Huang, 2013	Does not meet selection criteria
Huggins, 2014	Does not meet selection criteria
Ivanes, 2014	Does not meet selection criteria
Jaipaul, 2010	Does not meet selection criteria
Jarai, 2012	Does not meet selection criteria
Ji, 2015	Does not meet selection criteria
Jochheim, 2014	Does not meet selection criteria
Jo, 2015	Does not meet selection criteria
Kato, 2008	Does not meet selection criteria
Kian, 2006	Does not meet selection criteria
Kim, 2011	Does not meet selection criteria
Kim, 2012	Does not meet selection criteria
Kim, 2015	Does not meet selection criteria
Kiski, 2009	Does not meet selection criteria
Kiski, 2010	Does not meet selection criteria
Koo, 2013	Does not meet selection criteria
Kougias, 2014	Does not meet selection criteria
Kuhn, 2008	Does not meet selection criteria
Kwasa, 2014	Does not meet selection criteria
Lameire, 2006	Does not meet selection criteria
Laskey,2009	Does not meet selection criteria
Lee, 2014	Does not meet selection criteria
Lencioni, 2010	Does not meet selection criteria
Leung, 2014	Model predicts use of cardiac medication after development of PC-AKI, but does not predict risk of PC-AKI
Li, 2013	Does not meet selection criteria
Li, 2014	Does not meet selection criteria
Liebetrau, 2014	Does not meet selection criteria
Limbruno, 2014	Does not meet selection criteria
Lin, 2014	Does not meet selection criteria
Liu, 2012_1	Does not meet selection criteria
Liu, 2012_2	Does not meet selection criteria
Liu, 2013	Does not meet selection criteria
Liu, 2014	Does not meet selection criteria
Lodhia, 2009	Does not meet selection criteria
Lucreziotti, 2014	Does not meet selection criteria
Lui, 2012	Does not meet selection criteria
Macaulay, 2015	Does not answer research question, no multivariate analysis performed (n=7)
Madershahian, 2012	Does not meet selection criteria
Madershahian, 2012	Does not meet selection criteria
Madsen, 2009	Does not meet selection criteria
Mager, 2011	Does not meet selection criteria
Maioli, 2010	Does not meet selection criteria
Maioli, 2012	Does not meet selection criteria
Malyszko, 2009	Does not meet selection criteria
Marenzi, 2004_1	Does not meet selection criteria

Marenzi, 2004_2	Does not meet selection criteria
Matsushima, 2011	Does not meet selection criteria
McCullough, 2006_1	Does not meet selection criteria
McCullough, 2006_2	Does not meet selection criteria
McDonald, 2014_1	Does not meet selection criteria
McDonald, 2014_2	Does not meet selection criteria
Medalion, 2010	Does not meet selection criteria
Mehran, 2004	Does not meet selection criteria
Mehran, 2009	Does not meet selection criteria
Mehta, 2004	Does not meet selection criteria
Mekan, 2004	Does not meet selection criteria
Moos, 2013	Does not meet selection criteria
Moos, 2014	Does not show multivariate model that predicts risk factors of PC-AKI (but tests existing models)
Morabito, 2012	Does not meet selection criteria
Morcos, 2012	Does not meet selection criteria
Murakami, 2013	Does not meet selection criteria
Najjar (ea) 2002	Does not meet selection criteria
Naruse, 2012	Does not meet selection criteria
Ng, 2010	Does not meet selection criteria
Nikolsky, 2004	Does not meet selection criteria
Nikolsky, 2005	Does not meet selection criteria
Nozue, 2009	Does not meet selection criteria
Nyman, 2005	Does not meet selection criteria
Onuigbo, 2008	Does not meet selection criteria
Osman, 2014	Does not meet selection criteria
Owen, 2014	Does not meet selection criteria
Padhy, 2014	Does not meet selection criteria
Pahade, 2011	Does not meet selection criteria
Pakfetrat, 2010_1	Does not meet selection criteria
Pakfetrat, 2010_2	Does not meet selection criteria
Parra, 2004	Does not meet selection criteria
Patel, 2010	Review, not systematic and does not answer research question
Peguero, 2014	Does not meet selection criteria
Peng, 2015	Does not meet selection criteria
Piskinpasa, 2013	Combination of CAG and CT-scan patients (n=70), not analysed separately.
Polena, 2005	Does not meet selection criteria
Prasad, 2014	No multivariate analysis of risk factors for PC-AKI was performed
Rahman, 2005	Does not meet selection criteria
Raingruber, 2011	Does not meet selection criteria
Ranucci, 2013	Does not meet selection criteria
Raposeiras, 2015	Does not meet selection criteria
Raposeiras, 2015	Does not meet selection criteria
Ray, 2013	Does not meet selection criteria
Reuter, 2014	No multivariate analysis of risk factors for PC-AKI was performed
Sahin, 2014	Does not meet selection criteria
Saito, 2015	Does not meet selection criteria
Saritemur, 2014	Does not meet selection criteria
Sendur, 2013	Does not meet selection criteria
Sharma, 2013	Does not meet selection criteria
Shema, 2009	Does not meet selection criteria
Sidhu, 2008	Does not meet selection criteria
Skelding, 2007	Does not answer research question, validation of risk score
Spatz, 2012	Does not meet selection criteria
Spini, 2013	Does not meet selection criteria
Standstede, 2007	Does not meet selection criteria
Stermer, 2001	Does not meet selection criteria
Subedi, 2011	Does not meet selection criteria
Tan, 2013	Does not meet selection criteria
Taniguchi, 2013	Does not meet selection criteria

Thomsen, 2003	Does not meet selection criteria
Thomsen, 2009	Does not meet selection criteria
Toprak, 2006_1	Does not meet selection criteria
Toprak, 2006_2	Does not meet selection criteria
Toprak, 2007	Does not meet selection criteria
Trivedi, 2010	Does not meet selection criteria
Tziakas, 2014	Does not meet selection criteria
Ucar, 2014	Does not meet selection criteria
Ugur, 2014	Does not meet selection criteria
Umruddin, 2012	Does not meet selection criteria
Utsunomiyama, 2011	Studies risk factors for kidney insufficiency, not risk factors for development of PC-AKI after CT-scan
Victor, 2014	Does not meet selection criteria
Wacker-Gusmann, 2014	Does not meet selection criteria
Wang, 2011	Does not meet selection criteria
Weisbord, 2006	Does not meet selection criteria
Wessely, 2009	Does not meet selection criteria
Wi, 2013	Does not meet selection criteria
Yamamoto, 2013	Does not meet selection criteria
Zaytseva, 2009	Does not meet selection criteria

Exclusion after examination of full text (update 2017): Risk factors for PC-AKI

Author and year	**Redenen van exclusie**
Kanda, 2016	Does not meet selection criteria
Prasad, 2016.	Does not meet selection criteria
Abouzeid, 2016	Does not meet selection criteria
Agarwal, 201	Does not meet selection criteria
Azzalini, 2016	Does not meet selection criteria
Cernigliaro, 2016	Does not meet selection criteria
Briguori, 2016	Does not meet selection criteria
Chong, 2015	Does not meet selection criteria
de Francesco, 2015	Does not meet selection criteria
Dong, 2016	Does not meet selection criteria
Filomia 2016	Does not meet selection criteria
Guneyli, 2015	Does not meet selection criteria
Gurm, 2016.	Does not meet selection criteria
Subramaniam, 2016	Does not meet selection criteria
Ye, 2016 / Ye, 2017	Does not meet selection criteria
Zapata-Chica, 2015	Does not meet selection criteria
Hinson, 2017	Does not meet selection criteria
Hong, 2016	Does not meet selection criteria
Hsieh, 2016	Does not meet selection criteria
Huber, 2016	Does not meet selection criteria
Kanbay, 2017,	Does not meet selection criteria
Khaledifar, 2015	Does not meet selection criteria
Kim, 2015	Does not meet selection criteria
Komiyama, 2017	Does not meet selection criteria
Liu 2015	Does not meet selection criteria
McDonald 2015	Does not meet selection criteria
Nijssen, 2017	Does not meet selection criteria
Nyman, 2015	Does not meet selection criteria
Ortega, 2015	Does not meet selection criteria
Park, 2016	Does not meet selection criteria
Sato, 2015	Does not meet selection criteria
Shema, 2016	Does not meet selection criteria
Sigterman, 2016	Does not meet selection criteria
Salomon, 2015	Does not meet selection criteria
Tong, 2016,	Does not meet selection criteria
Turedi, 2016	Does not meet selection criteria
Usmiani, 2016	Does not meet selection criteria

Valette, 2017	Does not meet selection criteria
Vontobel, 2015	Does not meet selection criteria
Winther, 2016	Does not meet selection criteria
Xu, 2016	Does not meet selection criteria
Yang, 2014	Does not meet selection criteria
Zeller, 2016	Does not meet selection criteria

Exclusion after examination of full tekst: Measurement instruments for PC-AKI risk

Author and year	Reasons for exclusion
Aguiar, 2008	Letter to the editor
Akgullu, 2015	Does not fulfill selection criteria, no risk score is validated/developed
Balemans, 2012	Does not fulfill selection criteria, no risk score is validated/developed
Bartholemew, 2004	Already included in systematic review Silver, 2015
Benko, 2007	Not an original article (guideline)
Celik, 2015	The diagnostic properties of a laboratory analysis (contrast media volume toe GFR ratio) to predict PC-AKI are examined, not of a non-invasive method.
Chen, 2014	Already included in systematic review Silver, 2015
Chong, 2012	Does not fulfill selection criteria, no risk score is validated/developed
Crit, 2006	Does not fulfill selection criteria, no risk score is validated/developed
Davenport, 2013	The diagnostic properties of a laboratory analysis (different eGFR cut-off values) to predict PC-AKI are examined, not of a non-invasive method.
Davenport, 2013_1	The diagnostic properties of a laboratory analysis (different eGFR cut-off values) to predict PC-AKI are examined, not of a non-invasive method
Erselcan, 2009	The diagnostic properties of a laboratory analysis (eGFR by MDRD formula) to predict PC-AKI are examined, not of a non-invasive method.
Feldkamp, 2008	Narrative review
Fu, 2013	Already included in systematic review Silver, 2015
Gao, 2014	Already included in systematic review Silver, 2015
Ghani, 2009	Already included in systematic review Silver, 2015
Gurm, 2013	Already included in systematic review Silver, 2015
Holscher, 2008	Does not fulfill selection criteria, no risk score is validated/developed
Kim, 2011	Does not fulfill selection criteria, no risk score is validated/developed
Kooiman, 2010	Does not fulfill selection criteria, no risk score is validated/developed
Kowalczyk, 2007	Does not fulfill selection criteria, no risk score is validated/developed
Lepanto, 2011	Narrative review
Li, 2013	The diagnostic properties of a laboratory analysis (anemia) to predict PC-AKI are examined, not of a non-invasive method.
Liu, 2014	Already included in systematic review Silver, 2015
Maioli, 2011	Already included in systematic review Silver, 2015
Marenzi, 2004	Already included in systematic review Silver, 2015
Martainez – Lomakin, 2014	The diagnostic properties of a laboratory analysis (point of care creatinin test) to predict PC-AKI are examined, not of a non-invasive method.
McCullough, 2001	Narrative review
McCullough, 2007	Narrative review
McDonald, 2014	Does not fulfill selection criteria, no risk score is validated/developed
Mehran, 2004	Already included in systematic review Silver, 2015
Owen, 2014	Not an original article (guideline)
Pakfetrat, 2010	Does not fulfill selection criteria, no risk score is validated/developed
Rainburger, 2011	PC-AKI is not an outcome measure.
Saito, 2015	The diagnostic properties of a laboratory analysis (proteinuria and to predict PC-AKI are examined, not of a non-invasive method.
Sany, 2013	Does not meet selection criteria, no risk score is validated/developed
Skelding, 2007	Does not fulfill selection criteria, pre-defined outcome variables not reported
Skluzacek, 2003	The diagnostic properties of a laboratory analysis (eGFR) to predict PC-AKI are examined, not of a non-invasive method.
Tong, 1996	The diagnostic properties of a laboratory analysis (neutrophil gelatinase associated lipoprotein) to predict PC-AKI are examined, not of a non-invasive method.
Too, 2015	PC-AKI is not an outcome measure. The questionnaire's ability to predict eGFR is examined.

Tziakas, 2013	Already included in systematic review Silver, 2015
Wackecker-Guβmann, 2014	The diagnostic properties of a laboratory analysis (cystatin C) to predict PC-AKI are examined, not of a non-invasive method.
Wang, 2011	The diagnostic properties of a laboratory analysis (contrast media volume toe GFR ratio) to predict PC-AKI are examined, not of a non-invasive method.
Worasuwannarack, 2011	Article not found (Taiwanese journal)
Zahringer, 2014	PC-AKI is not an outcome measure. The questionnaire's ability to predict eGFR is examined.

Exclusion after examination of full text (update 2017): Measurement instruments for PC-AKI risk

Author and year	**Reasons for exclusion**
Akrawinthawong, 2015	Does not meet selection criteria
Ando, 2013	Does not meet selection criteria
Anonymous, 2015	Erratum
Balli, 2016	Does not meet selection criteria
Barbieri, 2016	Does not meet selection criteria
Chatterjee, 2017	Does not meet selection criteria
Garfinkle, 2015	Does not meet selection criteria
Goussot, 2015	Does not meet selection criteria
Grossman, 2017	Does not meet selection criteria
Gurm, 2016	Does not meet selection criteria
Hsieh, 2016	Does not meet selection criteria
Kim, 2015	Does not meet selection criteria
Li, 2016	Does not meet selection criteria
Liu, 2015	Does not meet selection criteria
Oksuz, 2015	Does not meet selection criteria
Osugi, 2016	Does not meet selection criteria
Ozturk, 2016	Does not meet selection criteria
Park, 2017	Does not meet selection criteria
Prasad, 2016	Does not meet selection criteria
Raposeiras-Roubin, 2013	Does not meet selection criteria
Sato, 2015	Does not meet selection criteria
Tao, 2016	Does not meet selection criteria
Victor, 2014	Does not meet selection criteria
Watanabe, 2016	Does not meet selection criteria
Xu, 2016	Does not meet selection criteria
Yin, 2017	Does not meet selection criteria
Yuan, 2017	Does not meet selection criteria
Brown, 2015	Does not meet selection criteria

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea et al.; 2007, BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher et al 2009, PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Eng, 2016	Yes	Yes	No	Yes	Yes	No	Yes	No	No

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs)**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table etc.)**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (e.g. Chi-square, I^2)?**
8. **An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Risk of bias table for intervention studies (randomized controlled trials)
Research question:

Study reference (first author, publication year)	**Describe method of randomisation**[1]	**Bias due to inadequate concealment of allocation?**[2] (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?**[4] (unlikely/likely/unclear)	**Bias due to loss to follow-up?**[5] (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?**[6] (unlikely/likely/unclear)
Chen, 2007	Not described "patients were randomly allocated"	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Jurado-Roman, 2014	Not described "patients were randomly assigned"	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Kooiman, 2014	Computer generated allocation sequence	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely
Maioli, 2011	Computer generated, open-label randomization block	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear

1. **Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.**
2. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..**
3. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
5. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear**

6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)
Research question:

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Bruce, 2009	Unlikely	Unclear	Unlikely	Likely
Davenport, 2013	Unlikely	Unclear	Unlikely	Likely
McDonald, 2013	Unlikely	Unclear	Unlikely	Likely

1. **Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.**
2. **2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.**
3. **Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.**

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

Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Eng, 2016 [individual study characteristics deduced from [1st	SR and meta-analysis of RCTs *Literature search up to June 2015* Study design: RCT [parallel]	Inclusion criteria SR: 1) RCTs that compared LOCM to IOCM with CIn incidence as the main outcome	Describe intervention: LOCM contrast administration Both ia and iv	Describe control: Iodixanol contrast administration Both ia and iv	End-point of follow-up: 72 hours For how many participants were no complete outcome data available?	Outcome measure-1 Defined as CIN Intra-arterial contrast administration Favors iodixanol: Relative risk (RR): 0.80 (0.64 – 1.01)	Facultative: Brief description of author's conclusion No differences were found in CIN risk among types of LOCM. Iodixanol

author, year of publication] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	<u>Setting and Country</u>: United States of America <u>Source of funding:</u> non-commercial	as the main outcome in patients having diagnostic imaging or image-based therapeutic procedures 2) CIN incidence is based on sCr or eGFR at baseline and within 72 hours of injection Exclusion criteria SR: 1) language other than English 2) mixed route of contrast administration *29 studies included* Groups comparable at baseline? Unclear			(intervention/control) Not described	I^2=43%, p=0.03) Intra-venous contrast administration Favors iodixanol: Relative risk (RR): 0.84 (0.42 – 1.71) I^2=29%, p=0.22)	had a slightly lower risk for CIN than LOCM, but the lower risk did not exceed the criterium for clinical importance. Level of evidence: GRADE (per comparison and outcome measure) including reasons for down/upgrading Most of the included studies GRADEd as Low (due to imprecision)

AKI: acute kidney injury; CI-AKI: contrast induced acute kidney injury; CIN: contrast induced nephropathy; CT: Computed Tomography; eGFR: estimated glomerular filtration ration; ia: intra-arterial; IOCM: iso-osmolar contrast medium; iv: intravenous; LOCM: low osmolair contrast medium; RCT: randomized controlled trial; sCr: serum creatinine;

Evidence table for intervention studies (randomized controlled trials and non-randomized *observational* studies [cohort studies, case-control studies, case series])[1]
This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy – otherwise the evidence table for studies of diagnostic test accuracy should be used.

Research question:

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Contrast administration versus no contrast administration for Computed Tomography							
Bruce, 2009	Type of study: retrospective observational Setting: in- and outpatients, multicentre study Country: United States of America Source of funding: not reported	Inclusion criteria: 1) age at least 18 years, 2) measurement of serum creatinine concentration within 30 days before CT, and creatinine measurement with result available within 3 days after the CT examination Exclusion criteria: 1) patient received iodinated contrast material as part of another procedure (e.g., cardiac catheterization) within 30 days before or 3 days after the reference CT examination. 2) patients with a preexisting status of undergoing long-term Dialysis 3) any record of dialysis within 30 days before or on the	Describe intervention (treatment/procedure/test): administration of isoosmolarcontrast medium (IOCM) (iodixanol) prior to Computed Tomography (CT)	Describe control (treatment/procedure/test): Unenchanced Computed Tomography	Length of follow-up: 3 days Loss-to-follow-up: Unclear, only patients that had a creatinine measurement at baseline and after 3 days were included in this retrospective study. Incomplete outcome data: As above	Outcome measures and effect size (include 95%CI and p-value if available): Acute kidney injury (=a 0.5 mg/dL increase in serum creatinine concentration or a 25% or greater decrease in estimated glomerular filtration rate within 3 days after CT) In all groups, the incidence of acute kidney injury increased with increasing baseline creatinine concentration. No significant difference in incidence of presumed contrast-induced kidney injury was identified between the	Authors' conclusion: We identified a high incidence of acute kidney injury among control subjects undergoing unenhanced CT. The incidence of creatinine elevation in this group was statistically similar to that in the isoosmolar contrast medium group for all baseline creatinine values and all stages of chronic kidney disease. These findings suggest that the additional risk of acute kidney injury accompanying administration of contrast medium (contrast-induced nephrotoxicity) may be overstated and that much of the

		day of the CT examination <u>N total at baseline</u>: Intervention: 337 Control: 6815 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 63 ± 16* *C: 59 ± 19* *Sex:* *I: 65% M* *C: 53% M* Groups comparable at baseline? Yes				isoosmolar contrast medium and the control groups. The incidence of acute kidney injury in the low-osmolar contrast medium cohort paralleled that of the control cohort up to a creatinine level of 1.8 mg/dL, but increases above this level were associated with a higher incidence of acute kidney injury.	creatinine elevation in these patients is attributable to background fluctuation, underlying disease, or treatment. Only patients that had a creatinine measurement at baseline and after 3 days were included in this retrospective study. IV administration of low-osmolar contrast medium (LOCM) (iohexol) to patients with a documented serum creatinine concentration of 2.0mg/dL or less if they did not have diabetes and to patients with a serum creatinine concentration of 1.5 mg/dL if they did have diabetes. We added a high-risk tier, allowing administration of iso-osmolar contrast medium (IOCM)

							(iodixanol) to nondiabetic patients with baseline creatinine values up to a maximum of 2.5 mg/dL and to diabetic patients with values up to a maximum of 2.0 mg/dL. Estimated GFR values are currently computed for all outpatients but have not supplanted serum creatinine concentration for contrast administration decisions.
Davenport, 2013	Type of study: retrospective observational Setting: in- and outpatients, multicentre study Country: United States of America Source of funding: not	Inclusion criteria: 1) CT studies performed in patients who had never undergone renal replacement therapy (eg, dialysis, renal transplantation), 2) patients had available data to permit calculation of the four-variable Modification of Diet in Renal Disease formula for eGFR, 3) patients had all of the	Describe intervention (treatment/procedure/test): contrast-enhanced CT examinations with LOCM	Describe control (treatment/procedure/test): CT examinations without contrast enhancement	Length of follow-up: 72 hours Loss-to-follow-up: Early post- CT SCr data were available for 1) 15 724 of 17 652 patients (89.1%) 0–24 hours after CT (7882 nonenhanced, 7842 contrast-enhanced),	Outcome measures and effect size (include 95%CI and p-value if available): Post CT-AKI (= difference between baseline and pre-CT SCr within 0.3 mg/dL and 50% of baseline) IV LOCM had a significant effect on the development of post-CT AKI (P = .04). This risk increased	Authors' conclusion: Intravenous LOCM is a nephrotoxic risk factor in patients with a stable eGFR less than 30 mL/min/1.73 m2, with a trend Toward significance at 30–44 mL/min/1.73 m^2. IV LOCM does not appear to be a nephrotoxic risk factor in patients

	reported	following SCr measurements available: *(a)* baseline SCr (the most recent SCr obtained more than 5 days before the index CT); *(b)* pre-CT SCr (the most recent SCr obtained between the time of the index CT and 5 days before); *(c)* at least one of three early post-CT SCr values (the first SCr obtained in each 24-hour period for the first 72 hours after the index CT). <u>Exclusion criteria</u>: 1) CT performed in a patient who had an earlier CT examination that met the inclusion criteria 2) missing data regarding contrast material administration 3) unstable renal function before the CT study 4) calculated eGFR was greater than 200 mL/min/1.73 m^2 5) patients lacked a 1:1			2) 12 941 of 17 652 patients (73.3%) 25–48 hours after CT (6450 nonenhanced, 6491 contrast-enhanced), 3) 10 213 of 17 652 patients (57.9%) 49–72 hours after CT (5091 nonenhanced, 5122 contrast-enhanced). <u>Incomplete outcome data</u>: As described above	with decreases in pre-CT eGFR (>60 mL/ min/1.73 m^2: odds ratio, 1.00; 95% confidence interval: 0.86, 1.16; 45–59 mL/min/1.73 m^2: odds ratio, 1.06; 95% confidence interval: 0.82, 1.38; 30–44 mL/min/1.73 m^2: odds ratio, 1.40; 95% confidence interval: 1.00, 1.97; <30 mL/min/1.73 m2: odds ratio, 2.96; 95% confidence interval: 1.22, 7.17)	with a pre-CT eGFR of 45 mL/min/1.73 m^2 or greater.

		propensity-matched control <u>N total at baseline</u>: Intervention: 8826 Control: 8826 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 59 ± 17* *C: 59 ± 18* *Sex:* *I: 48% M* *C: 48% M* Groups comparable at baseline? Yes					
McDonald, 2014	Type of study: retrospective observational Setting: in- and outpatients, multicentre study Country: United States of America Source of funding: not reported	<u>Inclusion criteria</u>: *1)* all patients who underwent an unenhanced (noncontrast group) or intravenous contrastenhanced (contrast group) abdominal, pelvic, and/or thoracic CT scan from January 1, 2000, to December 31, 2010, at our institution; *2)* who had one or more postscan SCr results during the time period of expected	Describe intervention (treatment/procedure/test): contrast-enhanced CT examinations Scan recipients were stratified with respect to their presumptive risk for AKI by baseline SCr level as follows: 1) low risk, SCr ,<1.5 mg/dL; 2) medium risk, SCr 1.5–2.0 mg/dL; 3) high risk, SCr > 2.0 mg/dL.	Describe control (treatment/procedure/test): CT examinations without contrast enhancement Scan recipients were stratified with respect to their presumptive risk for AKI by baseline SCr level as follows: 1) low risk, SCr ,<1.5 mg/dL; 2) medium risk, SCr 1.5–2.0 mg/dL; 3) high risk, SCr > 2.0 mg/dL.	<u>Length of follow-up</u>: 72 hours <u>Loss-to-follow-up</u>: Unclear, only patients that had a creatinine measurement at baseline and after 3 days were included in this retrospective study. <u>Incomplete outcome data</u>:	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=SCr ≥0.5 mg/dL above baseline) AKI risk was not significantly different between contrast and noncontrast groups in any risk subgroup after propensity score adjustment by using reported risk factors	Authors' conclusion: Following adjustment for presumed risk factors, the incidence of CIN was not significantly different from contrast material–independent AKI. These two phenomena were clinically indistinguishable with established SCr-defined criteria, suggesting that

		development of CIN (24–72 hours after CT-scanning) 3) who also had at least one baseline SCr result in the 24-hour window prior to scanning <u>Exclusion criteria</u>: 1) patients who had preexisting renal dialysis requirements; 2) did not have sufficient SCr data to permit detection of AKI; 3) patients who underwent multiple distinct CT-scans or percutaneous cardiac interventions with iodinated contrast material within a 14-day period <u>N total at baseline</u>: Intervention: 10686 Control: 10686 <u>Important prognostic factors</u>[2]: *For example* *age (range):* *I:* *Low risk: 62 (49-74)* *Medium risk: 71 (59-79)* *High risk: 69 (58-77)* *C:*			As above	of CIN 1) low risk: odds ratio [OR], 0.93; 95% confidence interval [CI]: 0.76,1.13; *P* = .47; 2) medium risk: odds ratio, 0.97; 95% CI: 0.81, 1.16; *P* = .76; 3) high risk: OR, 0.91; 95% CI: 0.66, 1.24; *P* = .58). Counterfactual analysis revealed no significant difference in AKI incidence between enhanced and unenhanced CT scans in the same patient (McNemar test: x2 =0.63, *P* = 0.43) (OR = 0.92; 95% CI: 0.75, 1.13; *P* = .46).	intravenous iodinated contrast media may not be the causative agent in diminished renal function after contrast material administration.

		Low risk: 63 (48-74) *Medium risk: 71 (59-80)* *High risk: 68 (56-77)* *Sex:* *I: % M* *Low risk: 48%* *Medium risk: 65%* *High risk: 63%* *C: % M* *Low risk: 49%* *Medium risk: 64%* *High risk: 64%* Groups comparable at baseline? Yes					
Hydration versus no hydration at contrast administration							
Chen, 2008	Type of study: RCT Setting: in- and outpatients, multicentre study Country: China Source of funding: not reported	<u>Inclusion criteria</u>: Patients with myocardial ischemia (angina or positive exercise treadmill) scheduled for percutaneous coronary intervention (PCI) in one of the three participating centers <u>Exclusion criteria</u>: (1) the coronary anatomy not suitable for PCI; (2) emergency coronary artery bypassgrafting (CABG) being required;	Describe intervention (treatment/procedure/test): sCr<1.5mg/dL: 0.45% saline given intravenously at a rate of 1 ml/kg/h starting from 12 h before scheduled time for coronary angiogram sCr ≥1.5mg/dL: 1) 0.45% saline given intravenously at a rate of 1 ml/kg/h starting from 12 h	Describe control (treatment/procedure/test): sCr<1.5mg/dL: No hydration sCr ≥1.5mg/dL: twice orally loading dose of 1200 mg NAC at 12 h before scheduled time for coronary angiogram and immediately after procedure	<u>Length of follow-up</u>: 6 months <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=increase in SCrN0.5 mg/dl at 48 h after PCI) sCr<1.5mg/dL: I: 6.7% C: 7.0% p>0.05 sCr ≥1.5mg/dL:	Author's conclusion: Patients with CIN and preexisting renal insufficiency had worse clinical outcomes. Hydration with 0.45% sodium chloride alone had no potential effect on the occurrence of CIN in patients with normal renal function. Combination of hydration with ATLS could reduce the

		(3) patients in chronic peritoneal or hemodialytic treatment; (4) acute myocardial infarction (AMI) at admission; (5) no written formal consent from patients <u>N total at baseline</u>: sCr<1.5mg/dL Intervention: 330 Control: 330 sCr ≥1.5mg/dL Intervention: 188 Control: 188 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* not reported *Sex: %M* sCr<1.5mg/dL 85% sCr ≥1.5mg/dL 82% Groups comparable at baseline? Unclear (patient data not reported for intervention and control group separately)	before scheduled time for coronary angiogram 2) twice orally loading dose of 1200 mg NAC at 12 h before scheduled time for coronary angiogram and immediately after procedure			I: 21.3% C: 34.0% P<0.001	incidence of CIN in patients at high risk. Groups comparable at baseline? Unclear (patient data not reported for intervention and control group separately)
Jurado-Roman,	Type of study: RCT	<u>Inclusion criteria</u>: patients who were	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	<u>Length of follow-up</u>:	Outcome measures and effect size	Authors' conclusion:

2014	Setting: in- and outpatients, single centre study Country: Spain Source of funding: not reported	admitted for STEMI and underwent a PPCI from July 2012 to November 2013 at our institution. Exclusion criteria: 1) end-stage renal failure requiring dialysis, 2) cardiac arrest, 3) severe heart failure (Killip III to IV) N total at baseline: Intervention: 204 Control: 204 Important prognostic factors[2]: *For example* *age ± SD:* *I:62 ± 14* *C: 64 ± 12* *Sex:* *I: 72% M* *C: 75% M* Groups comparable at baseline? Yes	Hydration: isotonic saline at an infusion rate of 1 ml/kg/h since the beginning of the procedure and during the following 24 hours. Prior to PPCI	No hydration Prior to PPCI	3 days Loss-to-follow-up: Not reported Incomplete outcome data: Not reported Crossover between study arms: 28% How this was handled in the data analysis is not reported. 74 patients changed from no hydration to hydration group because of sever hypotension 42 patients were changed from hydration to no hydration group because they developed heart failure	(include 95%CI and p-value if available): CIN (=a ≥25% or ≥0.5 mg/dl increase in serum a _25% or _0.5 mg/dl increase in serum) CIN was observed in 14% of patients: I: 11% C: 21% (p=0.016). In multivariate analysis, the only predictors of CIN were: 1) hydration (OR=0.29 [0.14 to 0.66]; p=0.003) 2) hemoglobin before the procedure (OR=0.69 [0.59 to 0.88]; p <0.0001)	In conclusion, intravenous saline hydration during PPCIreduced the risk of CIN to 48%. Given the higher incidence of CIN in emergentprocedures, and its morbidity and mortality, preventive hydration should be mandatory in them unless contraindicated. Crossover between study arms: 28% How this was handled in the data analysis is not reported.
Kooiman, 2014	Type of study: RCT Setting:in- and outpatients, single centre	Inclusion criteria: 1) Inpatients and outpatients with high clinical suspicion of acute PE requiring CTPA (i.e. Wells score ≥ 4 or	Describe intervention (treatment/procedure/test): Sodium bicarbonate hydration prior to CTPA	Describe control (treatment/procedure/test): No hydration prior to CTPA	Length of follow-up: 96 hours for laboratory parameters 2 months for	Outcome measures and effect size (include 95%CI and p-value if available): CI-AKI	Authors' conclusion: Our results suggest that preventive hydration could be safely withheld in

	Country: the Netherlands Source of funding: non-commercial	D-dimer levels > 500 ng mL^{-1}). 2) at least 18 years old 3) CKD (estimated glomerular filtration rate [eGFR] < 60 mL $min^{-1}/1.73\ m^2$ estimated by using the Modification of Diet in Renal Disease formula <u>Exclusion criteria</u>: 1) pregnancy, 2) previous contrast administration within the past 7 days, 3) documented allergy for iodinated contrast media, 4) hemodynamic instability (systolic blood pressure < 100 mm Hg) 5) participation in another trial <u>N total at baseline</u>: Intervention: 71 Control: 67 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 71 ± 13* *C: 70 ± 12*	250 mL intravenous 1.4% sodium bicarbonate 1 h before CTPA without hydration after CTPA.		clinical outcomes <u>Loss-to-follow-up</u>: Intervention: 2/71 (3%) 1 withdrew informed consent 1 died 24 hours after CTPA Control: 2/67 (3%) Lost to follow-up <u>Incomplete outcome data</u>: As above	(=creatinine increase > 25%/> 0.5 mg dL^{-1}) I: 5/71 (7%) C: 6/67 (9%) RR: 1.29, 95% confidence interval 0.41–4.03 None of the CI-AKI patients developed a need for dialysis.	CKD patients undergoing CTPA for suspected acute pulmonary embolism. This will facilitate management of these patients and prevents delay in diagnosis as well as unnecessary start of anticoagulant treatment while receiving volume expansion.

		Sex: *I: 48% M* *C: 52% M* Groups comparable at baseline? Yes					
Maioli, 2011	Type of study: RCT Setting: in- and outpatients, single centre Country: Italy Source of funding: not reported	<u>Inclusion criteria</u>: 1) patients with STEMI who were candidates for primary PCI <u>Exclusion criteria</u>: 1) contrast medium administration within the previous 10 days, 2) end-stage renal failure requiring dialysis, 3) refusal to give informed consent <u>N total at baseline</u>: Intervention: 154 Control: 153 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I:65 ± 13* *C: 64 ± 12* *Sex:* *I: 77% M* *C: 73% M* Groups comparable at baseline? Unclear	Describe intervention (treatment/procedure/test): Patients assigned to early hydration were administered a bolus of 3 mL/kg of sodium bicarbonate solution (154 mEq/L in dextrose and water) in 1 hour, starting in the emergency room, followed by infusion of 1 mL/kg per hour for 12 hours after PCI. Hydration rate was reduced to 0.5 mL/kg per hour in patients with left ventricular ejection fraction (EF) <40% or New York Heart Association class III–IV in both groups.	Describe control (treatment/procedure/test): No hydration prior to PCI.	<u>Length of follow-up</u>: 3 days <u>Loss-to-follow-up</u>: Intervention: 4/150 (3%) 1 had emergency procedure 3 no PCI Control: 3/153 (2%) 1 had emergency procedure 2 no PCI <u>Incomplete outcome data</u>: As above	Outcome measures and effect size (include 95%CI and p-value if available): CI-AKI (=an increase in serum creatinine of ≥25% or 0.5 mg/dL over the baseline value within 3 days after administration of the contrast medium) I: 12% C: 27% P<0.001 Death I: 3 (2%) C: 8 (5%) p>0.05 Hemofiltration I: 2 (1%) C: 1 (1%) p>0.05	Authors' conclusion: Adequate intravenous volume expansion may prevent CI-AKI in patients undergoing primary PCI. A regimen of preprocedure and postprocedure hydration therapy with sodium bicarbonate appears to be more efficacious than postprocedure hydration only with isotonic saline.

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures**
2. **Provide data per treatment group on the most important prognostic factors [(potential) confounders]**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders**

AKI: acute kidney injury; CI-AKI: contrast induced acute kidney injury; CIN: contrast induced nephropathy; CT: Computed Tomography; CTPA: Computed Tomogrpahy of the pulmonary artery; eGFR: estimated glomerular filtration ration; ia: intra-arterial; IOCM: iso-osmolar contrast medium; iv: intravenous; LOCM: low osmolair contrast medium; OR: odds ratio; PCI: Percutaneous Coronary Intervention; PE: pulmonary embolism; PPCI: primary Percutaneous Coronary Intervention; RCT: randomized controlled trial; RR: relative risk; sCr: serum creatinine; STEMI: ST-elevation myocardial infarction

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

Study reference	**Patient selection**	**Index test**	**Reference standard**	**Flow and timing**	**Comments with respect to applicability**
Duan, 2017	Was a consecutive or random sample of patients enrolled? Yes, consecutive Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Unclear 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	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias?	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias?	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias?	CONCLUSION Could the patient flow have introduced bias?	

	RISK: LOW	**RISK: LOW**	**RISK: LOW**	**RISK: LOW**	
Lian, 2017	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Unclear 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	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Abellas-Sequeiros, 2016	Was a consecutive or random sample of patients enrolled? Yes, consecutive Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Unclear 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	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by

				Were all patients included in the analysis? Yes	the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Araujo, 2016	Was a consecutive or random sample of patients enrolled? Yes, consecutive Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Unclear 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	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Chou, 2016	Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided?	Were the index test results interpreted without knowledge of the results of the reference standard? Unclear	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a	Are there concerns that the included patients do not match the review question? No Are there concerns that the

	Yes Did the study avoid inappropriate exclusions? Yes	If a threshold was used, was it pre-specified? Yes	results interpreted without knowledge of the results of the index test? Unclear	reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Lazaros, 2016	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Unclear 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	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias?	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias?	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias?	CONCLUSION Could the patient flow have introduced bias?	

	RISK: LOW	**RISK: LOW**	**RISK: LOW**	**RISK: LOW**	
Liu, 2016	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Unclear 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	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Aykan, 2013	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the	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

				analysis? Yes	match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Bartholomew, 2004	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
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Chen, 2014	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard?	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or

	Did the study avoid inappropriate exclusions? Yes	pre-specified? Unclear	knowledge of the results of the index test? Yes	Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Fu, 2012	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
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Gao, 2013	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
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Gurm, 2013	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis?	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question?

				Yes	No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Inohara, 2015	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
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Ivanes, 2014	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified?	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	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the

	Did the study avoid inappropriate exclusions? Yes	Unclear	index test? Yes	Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Ji, 2015	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Kul, 2014	Was a consecutive or random	Were the index test results	Is the reference standard likely	Was there an appropriate	Are there concerns that the

	sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes	interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Maioli, 2010	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No

	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Mehran, 2004	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
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Mizuno, 2015	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid	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? Unclear	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?	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question?

	inappropriate exclusions? Yes		Yes	Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Raposeiras-Roubín, 2013	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
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Sgura, 2010	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge	Is the reference standard likely to correctly classify the target	Was there an appropriate interval between index test(s)	Are there concerns that the included patients do not match

	Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes	and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Tziakas, 2013	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION:	CONCLUSION:	CONCLUSION:	CONCLUSION	

	Could the selection of patients have introduced bias? **RISK: LOW**	Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	Could the patient flow have introduced bias? **RISK: LOW**	
Tziakas, 2014	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Victor, 2014	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same	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

	Yes			reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Lin, 2014	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear	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? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	

Judgments on risk of bias are dependent on the research question: some items are more likely to introduce bias than others, and may be given more weight in the final conclusion on the overall risk of bias per domain:
Patient selection:

- **Consecutive or random sample has a low risk to introduce bias.**
- **A case control design is very likely to overestimate accuracy and thus introduce bias.**
- **Inappropriate exclusion is likely to introduce bias.**

Index test:

- **This item is similar to "blinding" in intervention studies. The potential for bias is related to the subjectivity of index test interpretation and the order of testing.**
- **Selecting the test threshold to optimise sensitivity and/or specificity may lead to overoptimistic estimates of test performance and introduce bias.**

Reference standard:

- **When the reference standard is not 100% sensitive and 100% specific, disagreements between the index test and reference standard may be incorrect, which increases the risk of bias.**
- **This item is similar to "blinding" in intervention studies. The potential for bias is related to the subjectivity of index test interpretation and the order of testing.**

Flow and timing:

- **If there is a delay or if treatment is started between index test and reference standard, misclassification may occur due to recovery or deterioration of the condition, which increases the risk of bias.**
- **If the results of the index test influence the decision on whether to perform the reference standard or which reference standard is used, estimated diagnostic accuracy may be biased.**
- **All patients who were recruited into the study should be included in the analysis, if not, the risk of bias is increased.**

Judgement on applicability:

Patient selection: there may be concerns regarding applicability if patients included in the study differ from those targeted by the review question, in terms of severity of the target condition, demographic features, presence of differential diagnosis or co-morbidity, setting of the study and previous testing protocols.

Index test: if index tests methods differ from those specified in the review question there may be concerns regarding applicability.

Reference standard: the reference standard may be free of bias but the target condition that it defines may differ from the target condition specified in the review question.

Evidence table for diagnostic test accuracy studies

Research question:

Study reference	**Study characteristics**	**Patient characteristics**	**Index test (test of interest)**	**Reference test**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Aykan, 2013	Type of study[1]: cohort study Setting: in- and	Inclusion criteria: Acute STEMI patients within 12 hours of symptom onset	Describe index test: SYNTAX score Comparator test[2]:	Describe reference test[3]: ≥25% increase of serum creatinine concentrations form baseline within 72 hours	Time between the index test en reference test: 72 hours For how many participants were no	Outcome measures and effect size (include 95%CI and p-value if available)[4]: Mehran: Sens: 73%	Internal validation only Patients with previous coronary artery bypass were excluded

[1] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

[2] Comparator test is vergelijkbaar met de C uit de PICO van een interventievraag. Er kunnen ook meerdere tests worden vergeleken. Voeg die toe als comparator test 2 etc. Let op: de comparator test kan nooit de referentiestandaard zijn.

	outpatients Country: Turkey Conflicts of interest: not reported	Exclusion criteria: Patients with previous coronary artery bypass N= 402 Prevalence: 32% Mean age ± SD: 63 ± 13 Sex: 76 % M	Mehran score	after PCI	complete outcome data available? NR Reasons for incomplete outcome data described? NR	Spec: 89% SYNTAX: Sens: 79% Spec: 89% Mehran: Cut-off value: 12.5 AUC: 0.68 (95% CI: 0.63 – 0.74, p<0.001) SYNTAX: Cut-off value: 31.5 AUC: 0.66 (95% CI: 0.60 – 0.71, p<0.001)	
Bartholomew, 2004	Type of study: cohort Setting: in- and outpatients Country: United States of America Conflicts of interest: commercial	Inclusion criteria: Coronary interventional procedures (single center) Exclusion criteria: - N= 10 481 Incidence of events: Derivation cohort: 2.8% Validation cohort: 1.2%	Describe index test: RCIN risk score	Describe reference test: ≥1.0mg/dL increase in serum creatinine from baseline within 48 hours of PCI	Time between the index test en reference test: 48 hours For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Outcome measures and effect size (include 95%CI and p-value if available): External validation Cohort 1: patients admitted for elective PCI N=2689 Discrimination: 0.59 Calibration: NR Cohort 2: patients admitted for elective or emergency PCI N=488 Discrimination: 0.58 Calibration: NR	

[3] De referentiestandaard is de test waarmee definitief wordt aangetoond of iemand al dan niet ziek is. Idealiter is de referentiestandaard de Gouden standaard (100% sensitief en 100% specifiek). Let op! dit is niet de "comparison test/index 2".

[4] Beschrijf de statistische parameters voor de vergelijking van de indextest(en) met de referentietest, en voor de vergelijking tussen de indextesten onderling (als er twee of meer indextesten worden vergeleken).

		Mean age ± SD: 65 ± 12 Sex: 67% M					
Chen, 2014	Type of study[4]: cohort study Setting: in- and outpatients Country: China Conflicts of interest: not reported	Inclusion criteria: patients receiving PCI, single center Exclusion criteria: - N=1500 ncidence of events: Derivation cohort: 16% Validation cohort: 17% Mean age ± SD: 64 ± 10 Sex:68 % M	Describe index test: "preprocedural risk scoring system"	Describe reference test: >0.5 mg/dL (44.2µmol/L) or 25% increase in serum creat8inine within 5 days of PCI	Time between the index test en reference test: 5 days For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Outcome measures and effect size (include 95%CI and p-value if available): Discrimination/calibration: 0.82 P=0.89 Risk score range associated with PC-AKI risk: Low: 5.3% Moderate: 19.9% High: 32.5% Very high: 59.5%	Internal validation only
Fu, 2012	Type of study[5]: cohort study Setting: in- and	Inclusion criteria: patients undergoing PCI, single center Exclusion	Describe index test: "risk score for contrast induced nephropathy in elderly patients"	Describe reference test: >0.5 mg/dL (44.2µmol/L) or 25% increase in serum creatinine within 48-72 hours of PCI	Time between the index test en reference test: 72 hours For how many participants were no	Outcome measures and effect size (include 95%CI and p-value if available): External validation Elderly patients at same	

[4] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

[5] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

	outpatients Country: China Conflicts of interest: not reported	criteria: - N= 668 Prevalence: 16% Mean age ± SD: 70 ± 6 Sex: 48% M			complete outcome data available? NR Reasons for incomplete outcome data described? NR	institution N=277 Discrimination: 0.79 Calibration: p>0.05	
Gao, 2004	Type of study[6]: cohort study Setting: in- and outpatients Country: China Conflicts of interest: not reported	Inclusion criteria: Coronary angiography or PCI, single center Exclusion criteria: - N=2764 Incidence of events: Derivation cohort: 5.5% Validation cohort: 5.0% Mean age ± SD: 60 ± 11 Sex: 71% M	Describe index test: "simple risk score for prediction of CIN" Comparator test: Mehran risk score	Describe reference test: >0.5 mg/dL or 25% increase in serum creatinine within 72 hours of PCI	Time between the index test en reference test: 72 hours For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Outcome measures and effect size (include 95%CI and p-value if available): Discrimination / calibration: 0.76 p>0.05 AUC: 1) "simple risk score": 0.75 (95% CI: 0.71 – 0.78) 2) Mehran: 0.57 (95%CI:0.54 – 0.60) Incidence of events: Derivation cohort: 4.6% Validation cohort: 4.2%	Internal validation only
Ghani, 2009	Type of study[7]: cohort study	Inclusion criteria: patients undergoing PCI,	Describe index test: "simple risk score for CIN"	Describe reference test: >0.5 mg/dL increase in serum creatinine within	Time between the index test en reference test: 48 hours	Outcome measures and effect size (include 95%CI and p-value if available):	Internal validation only

[6] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

	Setting: in- and outpatients Country: Kuwait Conflicts of interest: not reported	single center Exclusion criteria:- N= 247 Incidence of events: Derivation cohort: 5.5% Validation cohort: 5.0% Mean age ± SD: 63 ± 10 Sex: 68% M		48 hours of PCI	For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Risk score range associated with PC-AKI: <4: 9.2% 5-8: 32% 9-12: 54% >12: 84%	
Gurm, 2014	Type of study[8]: cohort study Setting: in- and outpatients Country: United States of America / the Netherlands	Inclusion criteria: patients undergoing PCI, multiple center Exclusion criteria: 1) patients on dialysis 2) patients with missing serum creatinine values N= 48001	Describe index test: "novel easy-to-use computational tool"	Describe reference test: >0.5 mg/dL increase in serum creatinine within 7 days of PCI	Time between the index test en reference test: 7 days For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Outcome measures and effect size (include 95%CI and p-value if available): AUC: 0.88 Risk score range associated with PC-AKI: Low: 0.5% Medium: 2.8% High: 13% Incidence of events: Derivation cohort: 2.6%	Internal validation only

[7] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

[8] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

	Conflicts of interest: not reported	Prevalence: 3% Mean age ± SD: 65 ± 12 Sex: NR				Validation cohort: 2.5%	
Inohara, 2014	Type of study[9]: cohort study Setting: in- and outpatients Country: Japan Conflicts of interest: not reported	Inclusion criteria: Exclusion criteria: N= 3957 Prevalence: 9% Mean age ± SD: 69 ± 11 Sex: 79% M	Describe index test: "pre-percutaneous cornary intervention risk model"	Describe reference test: An increase in serum creatinine of 50% or 0.3mg/dL compared with baseline	Time between the index test en reference test: 30 days For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Outcome measures and effect size (include 95%CI and p-value if available): External validation: N=1979 Discrimination: c-statistic 0.79	
Ivanes, 2014	Type of study[10]: cohort study Setting: in- and outpatients Country: France	Inclusion criteria: PCI, single center Exclusion criteria: - N=322 Prevalence:9% Mean age ± SD:	Describe index test: Mehran risk score	Describe reference test: ≥25% or 44.2µmol/L increase in serum creatinine following contrast administration	Time between the index test en reference test: 48 hours For how many participants were no complete outcome data available? NR	Outcome measures and effect size (include 95%CI and p-value if available): AUC: 0.59 CIN incidence: 9%	Internal validation only

[9] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

[10] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

	Conflicts of interest: not reported	64 ± 14 Sex: 66% M			Reasons for incomplete outcome data described? NR		
Jin, 2013	Type of study[11]: cohort study Setting: in- and outpatients Country: China Conflicts of interest: not reported	Inclusion criteria: Acute myocardial infarction patients undergoing PCI Exclusion criteria: - N= 1041 Prevalence: 14% Mean age ± SD: 68 ± 12 Sex: 52% M	Describe index test: Mehran risk score	Describe reference test: >0.5 mg/dL (44.2µmol/L) or 25% increase in serum creatinine within 48 hours of PCI	Time between the index test en reference test: 48 hours For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Outcome measures and effect size (include 95%CI and p-value if available): Risk score range associated with PC-AKI: Low: 12% Medium: 35% High: 36%	Internal validation only
Kul, 2015	Type of study[12]: cohort study Setting: in- and outpatients Country: Turkey	Inclusion criteria: patients with acute STEMI and undergoing emergency PCI Exclusion criteria: - N= 314	Describe index test: Zwolle risk score Comparator test: Mehran risk score	Describe reference test: >0.5 mg/dL or 25% increase in serum creatinine within 72 hours of PCI	Time between the index test en reference test: 72 hours For how many participants were no complete outcome data available? NR Reasons for incomplete	Outcome measures and effect size (include 95%CI and p-value if available): 1) Zwolle score >2 Sens: 76% Spec: 75% AUC: 0.85 2) Mehran score > 5 Sens: 71%	Internal validation only

[11] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

[12] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

	Conflicts of interest: not reported	Prevalence: 12% Mean age ± SD: 56 ± 11 Sex: 81% M			outcome data described? NR	Spec: 74% AUC:0.79	
Lin, 2015	Type of study[13]: cohort study Setting: in- and outpatients Country: Taiwan / Egypt Conflicts of interest: not reported	Inclusion criteria: PCI, single center (including emergency PCI) Exclusion criteria: - N= 516 Prevalence: 12% Mean age ± SD: 64 ± 11 Sex: 83% M	Describe index test: 1) "comprehensive risk score model", WHC model 2) Bartholomew model 3) Mehran model 4) Tziakas model 5) Ghain model	Describe reference test: >0.5 mg/dL (44.2µmol/L) or 25% increase in serum creatinine within 72 hours of PCI	Time between the index test en reference test: 72 hours For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Outcome measures and effect size (include 95%CI and p-value if available): AUC: 1) own model: 0.92 (95%CI: 0.88 – 0.96) 2) Bartholomew model 0.91 (95%CI: 0.87 – 0.95) 3) Mehran model: 0.90 (95%CI: 0.86 – 0.94) 4) Tziakas model: 0.70 (95%CI: 0.58 – 0.83) 5) Ghain model: 0.65 (95% CI: 0.53 – 0.78) External validation: n=241 Discrimination and calibration NR	
Maioli, 2010	Type of study[14]: cohort study Setting: in- and outpatients	Inclusion criteria: patients with an indication for coronary angiography or PCI, single center	Describe index test: Global Registry for Acute Coronary Events (GRACE) risk score Comparator test:	Describe reference test: >0.5 mg/dL (44.2µmol/L) or 25% increase in serum creatinine within 5 days of PCI	Time between the index test en reference test: 5 days For how many participants were no complete outcome data	Outcome measures and effect size (include 95%CI and p-value if available): GRACE Cut-off 160 Sens: 79%	Risk score range associated with PC-AKI risk: 0-1: 0% 2-3: 1% 4: 2% 5: 6%

[13] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

[14] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

	Country: Italy Conflicts of interest: not reported	Exclusion criteria: - N=1281 Prevalence: 3% Mean age ± SD: 69 ± 10 Sex: 67% M	Mehran risk score		available? NR Reasons for incomplete outcome data described? NR	Spec: 61% Mehran NR Incidence of events: Derivation cohort: 3.0% Validation cohort: NR AUC: 1) GRACE: 0.72 (0.3) and 0.69 (0.5) 2) Mehran: 0.78 (0.3) and 0.84 (0.5) External validation N=502 Discrimination and calibration NR	6: 12% 7: 19% 8: 24% 9: 36% 10: 50%
Marenzi, 2004	Type of study[15]: cohort study Setting: in- and outpatients Country: Italy Conflicts of interest: not reported	Inclusion criteria: patients referred for PCI for STEMI, single center Exclusion criteria: N= 218 Incidence of events: Derivation cohort: 19%	Describe index test: Marenzi risk score	Describe reference test: >0.5 mg/dL increase in serum creatinine within 5 days of PCI	Time between the index test en reference test: 5 days For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Outcome measures and effect size (include 95%CI and p-value if available): External validation N=891 Discrimination 0.57 and calibration NR	

[15] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

		Validation cohort: 14% M					
Mehran, 2004	Type of study[16]: cohort study Setting: in- and outpatients Country: United States of America Conflicts of interest: not reported	Inclusion criteria: patients referred for PCI, single center Exclusion criteria: - N= 5571 Prevalence: 14% Mean age ± SD: 64 ± 11 Sex: 71% M	Describe index test: Mehran risk score	Describe reference test: >0.5 mg/dL or 25% increase in serum creatinine within 48 hours of PCI	Time between the index test en reference test: 48 hours For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Outcome measures and effect size (include 95%CI and p-value if available): For Creatinine: Discrimination: 0.69 Validation: p=0.43 For eGFR: Discrimination: 0.70 Validation: p=0.42 External validation Cohort 1: patients undergoing cardiac catheterization or PCI, single center N=3945 Discrimination: 0.57 Calibration: NR Cohort 2: patients admitted for elective or emergency PCI, single center N=5571 Discrimination: 0.59 Calibration: NR	
Mizuno, 2014	Type of study[17]: cohort study	Inclusion criteria: patients undergoing a PCI	Describe index test: Mehran Risk score	Describe reference test: >0.5 mg/dL or 25% increase in serum	Time between the index test en reference test: 3 days	Outcome measures and effect size (include 95%CI and p-value if available):	Internal validation only

[16] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

	Setting: in- and outpatients Country: Japan Conflicts of interest: not reported	for STEMI, single center Exclusion criteria: - N= 102 Prevalence: 10% Mean age ± SD: 62 ± 14 Sex: 78 % M	(and red cell distribution width)	creatinine within 3 days of PCI	For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	AUC Mehran: 0.72 (0.54 – 0.90)	
Raposeiras-Roubín, 2013	Type of study[18]: cohort study Setting: in- and outpatients Country: Spain Conflicts of interest: not reported	Inclusion criteria: Patients with myocardial infarction after corronary angiography Exclusion criteria: - N=202 Prevalence: 28% Mean age ± SD: 63 ± 13	Describe index test: GRACE risk score	Describe reference test: ≥25% or ≥0.3mg/dL (or 0.5) rise in serum creatinine levels after 72 hours	Time between the index test en reference test: 72 hours For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Outcome measures and effect size (include 95%CI and p-value if available): GRACE risk score >140 was an independent predictor of CIN	Internal validation only

[17] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

[18] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

		Sex: 75% M					
Sgura, 2010	Type of study[19]: cohort study Setting: in- and outpatients Country: Italy Conflicts of interest: not reported	Inclusion criteria: patients undergoing PCI for STEMI, single center Exclusion criteria: - N= 891 Prevalence: 14% Mean age ± SD: 64 ± 13 Sex: 78% M	Describe index test: Mehran risk score Comparator test: Marenzi risk score	Describe reference test: >0.5 mg/dL (44.2µmol/L) or 25% increase in serum creatinine within 48 hours of PCI	Time between the index test en reference test: 48 hours For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Outcome measures and effect size (include 95%CI and p-value if available): AUC Mehran: 0.57 (95% CI 0.52 – 0.62) Marenzi: 0.57 (95% CI 0.51 – 0.62)	Internal validation only
Tziakas, 2013	Type of study[20]: cohort study Setting: in- and outpatients Country: Greece Conflicts of interest: not	Inclusion criteria: Elective or emergency PCI, single center Exclusion criteria: - N= 688 Incidence of events:	Describe index test: Tziakas score	Describe reference test: >0.5 mg/dL or 25% increase in serum creatinine within 48 hours of PCI	Time between the index test en reference test: 48 hours For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Outcome measures and effect size (include 95%CI and p-value if available): Calibration / discrimination: 0.76 p>0.05 External validation Cohort 1: PCI patient same single center N=200	

[19] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

[20] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

	reported	Derivation cohort: 10% Validation cohort: 14% Mean age ± SD: 64 ± 11 Sex: 74% M				Discrimination: 0.86 Calibration: NR Cohort 2: patients admitted for elective or emergency PCI, multiple centers (tertiary care) N=2689 Discrimination: 0.70 Calibration: p=0.18	
Tziakas, 2014	Type of study[21]: cohort study Setting: in- and outpatients Country: Greece Conflicts of interest: not reported	Inclusion criteria: PCI, elective or urgent, multiple centers Exclusion criteria: - N=2882 Prevalence: 16% Mean age ± SD: 61 ± 12 Sex: 70% M	Describe index test: Tziakas score	Describe reference test: >0.5 mg/dL or 25% increase in serum creatinine within 48 hours of PCI	Time between the index test en reference test: 48 hours For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Outcome measures and effect size (include 95%CI and p-value if available): AUC: 0.70 Risk score range associated with PC-AKI risk: ≤3: <20% >3: ≥20%	Internal validation only
Victor, 2014	Type of study[22]: cohort study Setting: in-	Inclusion criteria: patients with an indication for PCI, single center	Describe index test: "simple risk score for CIN"	Describe reference test: >0.5 mg/dL or 25% increase in serum creatinine within 48 hours of PCI	Time between the index test en reference test: 48 hours For how many	Outcome measures and effect size (include 95%CI and p-value if available): Sens: 94%	

[21] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

[22] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

	and outpatients Country: India Conflicts of interest: not reported	Exclusion criteria: - N=900 Incidence of events: Derivation cohort: 9.7% Validation cohort: 8.7% Mean age ± SD: 57 v 10 Sex: 84% M			participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Spec: 90% External validation N=300 Sens: 92% Spec: 82%	

Literature search description

Database	Search terms	Total
	1 exp contrast media/ae or (contrast adj3 iodine).ti,ab. or (contrast adj3 media).ti,ab. (18687) 2 exp Kidney Diseases/ or (((kidney or renal) adj2 (disease* or injur* or failure*)) or nephropath* or (renal adj2 (insufficienc* or function* or disease* or failure*))).ti,ab. (537305) 3 1 and 2 (3895) 4 (((contrast* or ci) adj2 (nephropath* or 'kidney injury' or aki or nephrotoxicity)) or ciaki).ti,ab. (1975) 5 3 or 4 (4504) 6 limit 5 to (yr="2000 -Current" and (dutch or english)) (2892) 7 risk assessment/mj or risk factors/mj or exp Renal Insufficiency/mj or Glomerular Filtration Rate/ (35215) 8 (((kidney or renal) adj2 function) or (risk adj2 (assessment or factor* or scor*)) or egfr or gfr or 'glomerular filtration rate').ti,ab. (559159) 9 exp contrast media/ad (14851) 10 7 or 8 (570621) 11 6 and 10 (1311) 12 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (248785) 13 11 and 12 (75) 14 (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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1510354) 15 11 and 14 (405) 16 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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 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] (2212779) 17 11 and 16 (574) 18 (recommend* or consensus*).ti. (47665) 19 guideline*.ab. /freq=2 (47817) 20 guideline*.ti. (54427) 21 Guideline/ or Practice Guideline/ or guidelines as topic/ or practice guidelines as topic/ (146566) 22 or/18-21 (216370) 23 11 and 22 (50) 24 13 or 15 or 17 or 23 (811) 25 13 or 23 (114) – 112 uniek 26 15 not 25 (359) – 353 uniek 27 25 or 26 (473) 28 17 not 27 (338) – 328 uniek	868

Literature search for tools to estimate risk of PC-AKI:

Database	Search terms	Total
Medline (OVID) 1995-now English, Dutch	1 exp Contrast Media/ or ((contrast adj3 iodine) or (contrast adj3 medi*)).ti,ab. or ESUR.ti,ab. (113073) 2 exp *Kidney Diseases/ or (((kidney or renal) adj2 (disease* or injur* or failure*)) or nephropath* or (renal adj2 (insufficienc* or function* or disease* or failure*))).ti,ab. (468614) 3 (((contrast* or ci) adj2 (nephropath* or 'kidney injury' or aki or nephrotoxicity)) or ciaki).ti,ab. (2004) 4 (1 and 2) or 3 (8499) 10 2 or 3 (468663) 11 8 and 10 (3) 12 limit 4 to (yr="1995 -Current" and (dutch or english)) (5270) 13 "Contrast Media"/ae [Adverse Effects] (8177) 14 "risk factor*".ab. /freq=3 (50816) 15 "Mass Screening"/ (86742) 16 "Risk Assessment"/ (192736) 17 (prediction or (risk adj3 (factor* or score* or marker*)) or screening).ti. (249759) 18 exp Questionnaires/ (343170) 19 (Questionnaire* or assessment*).ti. (220569) 20 Glomerular Filtration Rate/ or Creatinine/ or ("serum creatinine" or "glomerular filltration rate*").ti,ab. (96312)	311

	21 14 or 15 or 16 or 17 or 18 or 19 (988425) 22 12 and 21 (645) 23 exp "Sensitivity and Specificity"/ or (Sensitiv* or Specific*).ti,ab. or (predict* or ROC-curve or receiver-operator*).ti,ab. or (likelihood or LR*).ti,ab. or exp Diagnostic Errors/ or (inter-observer or intra-observer or interobserver or intraobserver or validity or kappa or reliability).ti,ab. or reproducibility.ti,ab. or (test adj2 (re-test or retest)).ti,ab. or "Reproducibility of Results"/ or accuracy.ti,ab. or Diagnosis, Differential/ or Validation Studies.pt. or *"Practice Guidelines as Topic"/ (4973682) 24 22 and 23 (323) 25 remove duplicates from 24 (311)	

Appendices to Chapter 5

Evidence tables

No literature search was performed for this chapter. The working group did not expect to find evidence for this question, since the clinical question could not be answered in a controlled study. Furthermore, the recommendations typically apply for the Dutch healthcare system.

Search conditions

No literature search was performed for this chapter. The working group did not expect to find evidence for this question, since the clinical question could not be answered in a controlled study. Furthermore, the recommendations typically apply for the Dutch healthcare system.

Appendices to Chapter 6

Evidence tables

Table: Exclusion after revision of full text

Author and year	Reason for exclusion
Akyuz. 2014	Patients with normal kidney function
Alessandri, 2014	Patients with normal kidney function
Cho, 2010	Does not fulfill selection criteria
Heguilen, 2013	Not using the most widely used PC-AKI definition of SC rise ≥25% or 44µmol/l
Koc, 2013	Patients with normal kidney function
Kong, 2012	Patients with normal kidney function
Kotlyar, 2005	Does not fulfill inclusion criteria (compares iv hydration with N-acetylcysteïne to hydration with placebo, not different hydration strategies)
Lawlor, 2007	Mixture of oral and intravenous hydration, compared to intravenous hydration alone
Mahmoodi, 2014	Patients with normal kidney function
Manari, 2014	The studied hydration infusion mixture is not used in Dutch clinical practice
Martin-Moreno, 2015	Patients with normal kidney function
Mueler, 2005	Does not fulfill inclusion criteria (no control group)
Pakfetrat, 2009	The studied hydration infusion mixture is not used in Dutch clinical practice
Taylor, 1998	Mixture of oral and intravenous hydration, compared to intravenous hydration alone
Thayssen, 2014	Patients with normal kidney function
Trivedi, 2003	Normal kidney function
Vashegani Ferahani, 2009	The studied hydration infusion mixture is not used in Dutch clinical practice
Wrobel, 2014	Did not define CIN/CI-AKI/PC-AKI
Yeghanehkah, 2014	The studied hydration infusion mixture is not used in Dutch clinical practice

Evidence table

Research question

Study reference (first author, publication year)	**Describe method of randomisation**[1]	**Bias due to inadequate concealment of allocation?**[2] (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?**[4] (unlikely/likely/unclear)	**Bias due to loss to follow-up?**[5] (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?**[6] (unlikely/likely/unclear)
Hydration versus no hydration								
Kooiman, 2014	Computer generated allocation sequence (stratified by hospital and renal function)	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely
Nijssen, 2017	Computer-generated using ALEA screening and enrolment application software.	Unlikely	Likely	Likely	Unlikely	Unlikely	Unlikely	Unlikely
Oral hydration								
Cho, 2010	Not decribed: “randomly assigned”	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Dussol, 2006	Computer generated randomization list	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Sodium bicarbonate short schedule versus saline short schedule for coronary angiography and/or percutaneous intervention								

Adolph, 2008	Computer-generated randomization schedule	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Boucek, 2013	Computer-generated randomization schedule with the use of numbered opaque envelopes containing identification of assigned medication	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Brar, 2008	Computer-generated randomization schedule	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Gomes, 2012	Not decribed: “randomly assigned”	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unlikely
Huber, 2016	Computer-generated randomization list	Unlikelu	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Manari, 2014	Computer generated balanced randomization list	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Ozcan, 2007	Not decribed: “randomly assigned”	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Ratcliffe, 2009	Not decribed: “randomization	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Likely	Unclear

	block"							
Recio-Mayoral, 2007	Not decribed: "randomly assigned"	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unlikely
Sodium bicarbonate short schedule versus saline long schedule for coronary angiography and/or percutaneous intervention								
Briguori, 2007	Computer-generated randomization schedule	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Castini, 2008	Computer-generated randomization table	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Hafiz, 2012	Random allocation table	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Klima, 2012	Sealed envelopes	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Lee, 2011	Interactive web response system, computer generated randomization, stratified by participating center	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Maioli, 2008	Computerized open-label assignment in blinded envelopes used in a consecutive fashion	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Nieto-Rios, 2014	Sealed opaque envelopes (random numbers table)	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear

Shavit, 2009	Not described	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Sodium bicarbonate versus saline: “other schedules” for coronary angiography and/or percutaneous intervention								
Chong, 2015	Block randomisation, stratified by site, using aweb-randomisation system or back-up randomisation envelopes.	Unlikely	Likely	Unclear	Unlikely	Unlikely	Unlikely	Unlikely
Motohiro, 2011	Computer-generated random numbers	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely
Tamura, 2009	Computer-generated random numbers	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely
Turedi, 2016	Computer-based block randomization.	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unlikely
Ueda, 2011	Computer-generated random numbers	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely
Sodium bicarbonate short schedule versus saline long schedule for computed tomography								
Kooiman, 2014	Computer-generated allocation sequence	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely
Controlled diuresis								
Brar, 2014	Computer-generated concealed	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely

	randomisation schedule							
Barbanti, 2015	Randomization based on computer generated codes	Unlikely	Likely	Likely	Unlikely	Unlikely	Unlikely	Unlikely
Briguori, 2011	Computer-generated randomisation list	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Marenzi, 2012	Computer-generated random numbers	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Qian, 2016	"randomly assigned"	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Usmiani, 2015	"randomly assigned"	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Usmiani, 2016	Randomly subdivided	Unlikely	Likely	Likely	Unlikely	Unlikely	Unclear	Unlikely
Visconti, 2016	Prospective, non-randomised study	Likely	Unclear	Unclear	Unclear	Unlikely	Unclear	Unclear

7. Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.

8. Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..

9. Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.

10. Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.

11. If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear

12. Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series])1
This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy – otherwise the evidence table for studies of diagnostic test accuracy should be used.

Research question

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Hydration versus no hydration							
Kooiman, 2014	Type of study: randomized controlled trial Setting: emergency patients, multiple centers, both in- and outpatients Country: the Netherlands Source of funding: non-commercial	Inclusion criteria: 1) adult patients ≥18 years with a clinical suspicion of a pulmonary embolis requiring computed tomography-pulmonary angiography (CTPA) 2) chronic kidney disease (CKD): eGFR <60mL/min/1.73m^2 Exclusion criteria: 1) pregnancy 2) previous contrast administration within past 7 days 3) documented allergy for iodinated contrast media	Describe intervention (treatment/procedure/test): Withholding hydration prior to CTPA	Describe control (treatment/procedure/test): 250mL iv 1.4% sodium bicarbonate 1 hour before CTPA	Length of follow-up: 96 hours Loss-to-follow-up: 3/138 (2.2%) 2 lost to follow-up 1 died Incomplete outcome data: As above	Outcome measures and effect size (include 95%CI and p-value if available): CI-AKI (= creatinine increase >25% / >0.5mg/dL) I: 6 (9%) C: 5 (7%) RR: 1.29, 95% CI: 0.41 – 4.03 None of the patients developed a need for dialysis	Authors' conclusion: Our results suggest that preventive hydration could be safely withheld in CKD patients undergoing CTPA for suspected acute pulmonary embolism.

		4) hemodynamic instability (systolic blood pressure <100mmHg) 5) earlier participation in samen trial N total at baseline: Intervention: 67 Control: 71 Important prognostic factors[2]: *For example* *age ± SD:* *I: 70 ± 12* *C: 71 ± 13* *Sex:* *I: 52% M* *C: 48% M* *eGFR ± SD:* *I: 50 ± 16* *C: 48 ± 15* Groups comparable at baseline? Yes					
Nijssen, 2017 (AMACING)	Type of study: randomized controlled trial Setting: elective	Inclusion criteria: 1) eGFR: 45-59 mL/min/1.73m^2 combined with either diabetes, or at least two	Describe intervention (treatment/procedure/test): Prophylactic hydration protocols according to current guidelines:	Describe control (treatment/procedure/test): No prophylactic treatment.	Length of follow-up: 2-6 days Loss-to-follow-up:	Outcome measures and effect size (include 95%CI and p-value if available):	Authors' conclusion: *'We found no prophylaxis to be non-inferior and*

	patients, one university hospital Country: the Netherlands Source of funding: Stichting de Weijerhorst	predefined risk factors (age>75y; anaemia defined as haematocrit values <0.39L/L for men, and <0.36L/L for women; cardiovascular disease; non-steroidal anti-inflammatory drug; or diuretic nephrotoxic medication). Exclusion criteria: 1) Inability to obtain informed consent; 2) eGFR lower than 30mL per min/1.73m^2; 3) renal replacement therapy; 4)emergency procedures; 5) intensive care patients; 6) known inability to perform primary endpoint data collection; 7) no referral to prophylactic hydration; 8) participation in	Standard protocol intravenous 0.9% NaCl 3–4 mL/kg per h during 4 h before and 4 h after contrast administration; long protocol intravenous 0.9% NaCl 1 mL/kg per h during 12 h before and 12 h after contrast administration.		I: 68/328 C: 25/332 Incomplete outcome data: As above	CI-AKI (25% or 44 µmol/L within 2–6 days of contrast exposure) I:8 (2.7%) C: 8 (2.6%) P=0.417 No hydration was cost-saving relative to hydration. No haemodialysis or related deaths occurred within 35 days.	*cost-saving in preventing contrast-induced nephropathy compared with intravenous hydration according to current clinical practice guidelines.'*

		other RCT; and 9) isolation due to infection control <u>N total at baseline</u>: Intervention: 328 (I1: 328, I2: 296) Control: 332 (C1: 332, C2: 307) <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 71.9 ± 9.3* *C: 72.6 ± 9.3* *Sex:* *I: 59% M* *C: 64% M* *Baseline SCr:* *I:118.7±28*μmol/L *C:117.7±25*μmol/L Groups comparable at baseline? Yes					
Oral hydration							
Cho, 2010	Type of study: randomized controlled trial Setting: elective patients, one hospital	<u>Inclusion criteria</u>: 1) patients 18 years or older with stable serum creatinine levels of at least 1.1mg/dL or estimated creatinine clearance less than	Describe intervention (treatment/procedure/test): 1) oral hydration with 500mL of water to be started 4 hours prior to contrast exposure and stopped 2 hours prior to procedure followed by oral hydration with	Describe control (treatment/procedure/test): 1) pretreatment with a 3mL/kg bolus of intravenous saline solution (154mEq/L) over 1 hour priori to contrast exposure Intravenous infusion of 1mL/kg for	<u>Length of follow-up</u>: 72 hours <u>Loss-to-follow-up</u>: Not reported <u>Incomplete</u>	Outcome measures and effect size (include 95%CI and p-value if available): CIN (= >25% increase in sCr from baseline	Authors' hydration: Oral hydration with or without sodium bicarbonate prior to and following CAG is not

	Country: United States of America Source of funding: not reported	60mL/min scheduled for diagnostic, elective angiography <u>Exclusion criteria</u>: 1) serum creatinine levels >8.0mg/dL 2) change in serum creatinine levels of at least 0.5mg/dL during the previous 24 hours 3) pre-existing dialysis 4) multiple myeloma or other myeloproliferative disease 5) current decompensated heart failure or significant change in NYHA 6) current myocardial infarction 7) symptomatic hypokalaemia 8) uncontrolled hypertension 9) exposure to radiocontrast within 7 days of enrolment into this study 10) emergency	600mL water postprocedure 2) oral hydration with 500mL of water to be started 4 hours prior to procedure and stopped 2 hours prior to contrast exposure, with the addition of 3.9g (46.4mEq) of oral sodium bicarbonate to be given 20 minutes prior to contrast exposure followed by oral hydration with 600mL of water and 1.95g (30.4mEq) of oral sodium bicarbonate 2 hours and 4 hours after the initial dose	6 hours after procedure 2) pretreatment with a 3mL/kg bolus of intravenous sodium biacrbonate solution (154mEq/L) over 1 hour priori to contrast exposure Intravenous infusion of 1mL/kg for 6 hours after procedure	<u>outcome data</u>: Not reported	or an absolute increase of 0.5mg/dL from baseline at 72 hours following exposure to radio-contrast) I1: 1/22 I2: 1/22 C1: 6/27 C2: 2/21 p>0.05 There were no in-hospital mortalities during this study. Length of hospital stay did not differ significantly between groups.	inferioir to intravenous hydration and sodium bicarbonate with respect to CIN; and to date, offers an equivalent and practical approach in preventing a decline in renal functionafter contrast exposure without accuring additional delay in hospital days or in-hospital mortality,

		catheterisation 11) allergy to radiographic contrast 12) pregnancy 13) administration of mannitol, feoldapam or NAC during the time of the study 14) exacerbation of chronic obstructive pulmonary disease 15) serum bicarbonate greater than 28eEw/L and sodium less than 133mEq/L <u>N total at baseline</u>: Intervention: 43 (I1: 22, I2: 22) Control: 48 (C1: 27, C2: 21) <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I1: 81 ± 7* *I2: 79 ± 2* *C1: 77 ± 8* *C2: 78 ± 9* *Sex:* *I1: 45% M* *I2: 38% M*					

		C1: 63% M *C2: 52* *Baseline SCr:* *I1: 1.38* *I2: 1.31* *C1: 1.38* *C2: 1.41* Groups comparable at baseline? Yes					
Dussol, 2006	Type of study: randomized controlled trial Setting: elective patients, one university hospital Country: France Source of funding: non-commercial	<u>Inclusion criteria</u>: 1) patients referred for any radiological procedures necessitating a contrast medium injection and who had a baseline Cockcroft clearance between 15-60ml/min 2) either chronic renal failure and on a kidney graft <u>Exclusion criteria</u>: 1) <18 years old 2) women of child-bearing age not using contraception or breast feeding 3) patients with heart failure and ejection fraction <30% 4) uncontrolled	Describe intervention (treatment/procedure/test): NaCl 1g/10kg/day per os for 2 days	Describe control (treatment/procedure/test): 0.9% saline iv 15ml/kg for 6 hours before the procedure	<u>Length of follow-up</u>: 48 hours <u>Loss-to-follow-up</u>: Not reported per group separately, in total 3/315 (1%) lost to follow-up <u>Incomplete outcome data</u>: As above	Outcome measures and effect size (include 95%CI and p-value if available): CIN (= increase in the baseline sCr concentration of at least 44µmol/L (0.5mg/dL) within 48 hours after the injection of contrast media) I: 5/76 (7%) C: 4/77 (5%) p>0.05 None of the patients had fluid overload	Authors' conclusion: Oral saline hydration was as efficient as intravenous saline hydration for the prevention of CIN in patients with stage 3 renal diseases.

		arterial hypertension 5) obvious extracellular overhydration 6) respiratory depression 7) known prior intolerance to theophylline or furosemide 8) previous exposure to contrast media in the 14 days before randomization 9) unwilling or unable to provide informed consent 10) adequate time prior to contrast media injection was not available to perform the study procedure 11) if sCr measurements varied by >10% in the previous weeks before referral <u>N total at baseline</u>: Intervention: Control: <u>Important prognostic factors</u>[2]:					

		For example *age ± SD:* *I: 63 ± 15* *C: 64 ± 11* *Sex:* *I: 66% M* *C:75 % M* *eGFR ± SD:* *I: 38 ± 13* *C: 33 ± 11* Groups comparable at baseline? Yes					
Sodium bicarbonate short schedule versus saline short schedule for coronary angiography and/or percutaneous intervention							
Adolph, 2008	Type of study: randomized controlled trial Setting: elective patients Country: Germany Source of funding: not reported	<u>Inclusion criteria</u>: 1) patients >18 years with baseline serum creatinine concentration greater than 106µmol/L (1.2mg/dL) undergoing elective diagnostic or interventional coronary angiography <u>Exclusion criteria</u>: 1) acute myocardial infarction 2) allergies to trial medication 3) exposure to contrast	Describe intervention (treatment/procedure/test): Sodium bicarbonate 154mEq/L in 5% dextrose solution 2ml/kg body weight/hour for 2 hours before And 1ml/kg body weight/hour during and for 6 hours after contrast administration	Describe control (treatment/procedure/test): Sodium chloride 154 mEq/L in 5% dextrose solution 2ml/kg body weight/hour for 2 hours before And 1ml/kg body weight/hour during and for 6 hours after contrast administration	<u>Length of follow-up</u>: 2 days <u>Loss-to-follow-up</u>: 1 patient (refused follow-up) <u>Incomplete outcome data</u>: 3/145 (2%) 2 patients had an emergency coronary bypass and pulmonary edema	Outcome measures and effect size (include 95%CI and p-value if available): CIN (= elevation of sCr concentration >0.5mg/dL (44µmol/L) or 25%above baseline between day 0 and days 1 or 2 after contrast axposure) I: 4.2% C: 2.7% P=0.61 Dialysis for acute renal failure was	Authors' conclusion: Renal Insufficiency following radiocontrast exposure demonstrates a homogenously low rate of CIN after exposure to non-ionic, iso-osmolar iodixanol regardless of the use of either bicarbonate sodium or sodium chloride solution for volume supplementation.

		mediumwithin the last 7 days 4) thyroid dysfunction 5) pregnancy 6) uncontrolled hypertension 7) life-limiting concomitant disease 8) pulmonary edema 9) chronic dialysis 10) administration of dopamine, mannitol, fenoldopam or NAC during the study <u>N total at baseline</u>: Intervention: 71 Control: 74 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 70 ± 8* *C: 73 ± 7* *Sex:* *I: 75% M* *C: 81% M* *sCr (mg/dL ± SD)* *I: 1.54 ± 0.51* *C: 1.57 ± 0.36*			1 patient refused follow-up	not required	

		Groups comparable at baseline? Yes					
Boucek, 2013	Type of study: RCT Setting: elective inpatients, one hospital Country: Czech Republic Source of funding: commercial	<u>Inclusion criteria</u>: 1) presence of diabetes mellitus 2) renal function impairment (screening serum creatinine _100 mmol/L), 3) age of ≥18 years 4) a planned procedure with intra-arterial or intravenous use of contrast <u>Exclusion criteria</u>: 1) endstage renal disease (screening serum creatinine _500 mmol/L, 2) chronic dialysis treatment or presence of kidney transplant), 3) pre-planned dialysis following the contrast-involving procedure, 4) emergency type of procedure, acute kidney injury	Describe intervention (treatment/procedure/test): 1.4% sodium bicarbonate in 5% glucose 3ml/kg/hour 1 hour before contrast administration (limited to a maximum of 330mL) 1mL/kg/hour 6 hours after contrast administration (limited to a maximum of 660mL)	Describe control (treatment/procedure/test): 0.9% saline in 5% glucose 3ml/kg/hour 1 hour before contrast administration (limited to a maximum of 330mL) 1mL/kg/hour 6 hours after contrast administration (limited to a maximum of 660mL)	<u>Length of follow-up</u>: 2 days – laboratory parameters 1 month – clinical parameters <u>Loss-to-follow-up</u>: Intervention: 3/61 (5%) Reasons not described Control: 3/59 (5%) Reasons not described <u>Incomplete outcome data</u>: As above	Outcome measures and effect size (include 95%CI and p-value if available): CIN (= sCr increase of ≥25% and/or 44µmol/L (0.5mg/dL) within 2 days foillowing administration of contrast) I: 7 (12%) C: 5 (9%) P=0.76 Incidence rate ratio: 1.35 (95% CI: 0.37 – 5.41) No patients died or experienced severe kidney injury with need for acute dialysis treatment.	Authors' conclusion: In diabetic patients with renal function impairment sodium bicarbonate does not confer protection against contrast-induced nephropathy greater than sodium chloridebased hydration.

		(serum creatinine increase _50 mmol/L during the previous 24-h period), 5) volume overload with left ventricular failure, 6) uncontrolled hypertension (systolic BP _180 or diastolic BP _110 mmHg), 7) hemodynamic instability (systolic BP <90 and diastolic BP <50 mmHg), 8) contrast use in the previous 48-h period, 9) multiple myeloma, 10) pregnancy or breastfeeding 11) pre-planned use of any other measure for CIN prevention apart from the NaCl or NaHCO3 infusions <u>N total at baseline</u>: Intervention: 61 Control: 59					

		Important prognostic factors[2]: *For example* *age ± SD:* *I: 63 ± 11* *C: 67 ± 10* *Sex:* *I: 75% M* *C: 75% M* *eGFR (mL/min/1.73m^2) ± SD* *I: 44 ± 19* C: 25 *± 17* Groups comparable at baseline? Yes					
Brar, 2008	Type of study: randomized controlled trial Setting: elective patients, one hospital Country: United States of America Source of funding: commercial	Inclusion criteria: 1) an estimated glomerular filtration rate (GFR) of 60 mL/min per 1.73m2 or less, 2) age 18 years or older, 3) at least 1 of the follwing: -diabetes mellitus, -history of congestive heart failure, -hypertension (140/90 mm Hg treatment with an antihypertensive	Describe intervention (treatment/procedure/test): 1.4% sodium bicarbonate iv infusion Infusion was begun 1 hour prior to the start of contrast administration at3mL/kg for1hour, decreased to 1.5 mL/kg per hour during the procedure and for 4 hours following completion of theprocedure.Forpatientsweighing more than 100 kg, the bolus and infusion rate were limited to those used for	Describe control (treatment/procedure/test): 0.9% saline iv infusion Infusion was begun 1 hour prior to the start of contrast administration at3mL/kg for1hour, decreased to 1.5 mL/kg per hour during the procedure and for 4 hours following completion of theprocedure.Forpatientsweighing more than 100 kg, the bolus and infusion	Length of follow-up: 2-3 days for laboratory parameters 6 months for clinical effects Loss-to-follow-up: Intervention: 17 (10%) Excluded 1 Did not undergo coronary angiography	Outcome measures and effect size (include 95%CI and p-value if available): ≥25% reduction in estimated eGFR I: 21/158 (13% C: 24/165 (15%) Absolute difference: 1.3, 95% CI: -6.3 to 8.8, p=0.75 Serum creatinine >25% or >0.5mg/dL	Authors' conclusion: The results of this study do not suggest that hydration with sodium bicarbonate is superior to hydration with sodium chloride for the prevention of contrast medium–induced nephropathy in patients with moderate to

		medication), -age older than 75 years <u>Exclusion criteria</u>: 1) inability to obtain consent, 2) receipt of a sodium bicarbonate infusion prior to randomization, 3) emergency cardiac catheterization, 4) intra-aortic balloon counterpulsation, 5) dialysis, 6) exposure to radiographic contrast media within the preceding 2 days, 7) allergy to radiographic contrast media, 8) acutely decompensated congestive heart failure, 9) severe valvular abnormality (eg, severe aortic stenosis or mitral regurgitation), 10) single	patients weighing100kg	rate were limited to those used for patients weighing100kg	16 Did not have estimated GFR data 1-4 d after procedure Control: 13 (7%) Excluded 2 Did not undergo coronary angiography 11 Did not have estimated GFR data 1-4 d after procedure <u>Incomplete outcome data</u>: As above for laboratory paramters. All patients were followed up for clinical events.	increase I: 26/158 (17%) C: 30/165 (18%) Absolute difference: 1.7, 95% CI: -6.5 to 10.0, p=0.78 30-day mortality I: 3/175 (2%) C: 3/178 (2%) p>0.05 6-month mortality I: 34% C: 2% P=0.54 6-month start of dialysis I: 2/175 (1%) C: 4/178 (2%) P-value not reported	severe chronic kidney disease who are undergoing coronary angiography.

		functioning kidney, 11) history of kidney or heart transplantation, 12) change in estimated GFR of 7.5% or more per day or a cumulative change of15%or more over the prior 2 or more days <u>N total at baseline</u>: Intervention: 175 Control: 178 <u>Important prognostic factors</u>[2]: *For example* *age (IQR range)* *I: 71 (65-75)* *C: 71 (65-76)* *Sex:* *I: 65% M* *C: 62% M* Groups comparable at baseline? Yes					
Gomes, 2012	Type of study: randomized controlled trial Setting: elective patients, 6	<u>Inclusion criteria</u>: 1) patients at moderate to high risk for developing CIN who were referred for elective coronary	Describe intervention (treatment/procedure/test): 154 mEq/l of sodium bicarbonate in 5% dextrose and H_2O	Describe control (treatment/procedure/test): 0.9% saline infusion 3 mL/ kg/ h for 1 hour immediately	<u>Length of follow-up</u>: 48 hours <u>Loss-to-follow-up</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN	Authors' conclusion: Hydration with sodium bicarbonate was not superior to

	difference centres Country: Brazil Source of funding: none reported	angiography or PCI at 6 centers 2) serum creatinine ≥ 1.2 mg/dL or glomerular filtration rate (GFR) <50 mL/min <u>Exclusion criteria</u>: 1) age <18 years, 2) use of radiographic contrast media during the last 21 days, 3) history of dialysis, 4) cardiac insufficiency class III-IV NYHA, 5) emergency procedures <u>N total at baseline</u>: Intervention: 150 Control: 151 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 64 ± 12* *C: 65 ± 12* *Sex:* *I: 69% M* *C: 75% M*	3 mL/ kg/ h for 1 hour immediately before contrast injection same fluid at a rate of 1 mL/kg/h during contrast exposure and for 6 hours after the procedure	before contrast injection same fluid at a rate of 1 mL/kg/h during contrast exposure and for 6 hours after the procedure	<u>Incomplete outcome data</u>: Not reported	(=an increase in serum creatinine ≥ 0.5 mg/dL 48 hours after exposure to contrast medium) I: 9/150 (6%) C: 9/151 (6%) P=0.97 Dialysis: I: 0% C: 0% P=1.00 Death: I: 3% C: 5% P=0.81	saline to prevent contrast media induced nephropathy in patients at risk undergoing cardiac catheterization.

		eGFR ± SD *I: 51 ± 13* *C: 52 ± 13* Groups comparable at baseline? Yes					
Huber, 2016	Type of study: randomized controlled Setting: single-center university hospital Country: Germany Source of funding: institutional support	Inclusion criteria: <u>1) >18 years;</u> <u>2) increased risk of CIN undergoing administration of CM.</u> High risk was defined by a serum creatinine level ≥1.1 or ≥0.8 mg/dL plus an additional risk factor like diabetes mellitus, renal failure in past medical history, or nephrotoxic medication (aminoglycoside, vancomycin, amphotericin B, and diuretic). <u>Exclusion criteria:</u> 1) pre-existing renal replacement therapy; 2) unstable serum creatinine levels (difference of more than _0.4 mg/dL	Describe intervention (treatment/procedure/test): Group B received bicarbonate infusion with 200mg theophylline.	Describe control (treatment/procedure/test): Control group S received sodium chloride infusion with 200mg theophylline.	<u>Length of follow-up</u>: 48h after CM <u>Loss-to-follow-up</u>: I:14/91 C: 14/94 <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN as a raise in serum creatinine of _25% or _0.5 mg/dL within 48 h after contrast application I: 1/74 (1.4%) C: 7/78 (9%) P=0.039 Dialysis: I: 9% C: 17% P=0.189	Authors' conclusion: *'In patients at increased risk of CIN receiving prophylactic theophylline, hydration with sodium bicarbonate reduces contrast-induced renal impairment compared to hydration with saline.'*

		within 3 days before contrast application); 3) contraindi-cations for theophylline or sodium bicarbonate (allergies, tachycardia, alkalosis, and hypokalemia); and; 4) additional interventions that might influence renal function. <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 64.4 ± 15.7* *C: 66.1 ±13.3* *Sex:* *I: 59.5% M* *C: 66.7% M* *Baseline SCr:* *I:1.25± 0.69 mg/dL* *C:1.38± 0.65 mg/dL* Groups comparable at baseline? Yes					

Manari, 2014	Type of study: randomized controlled Setting: emergency patients, multicentre trial Country: Italy Source of funding: not reported	Inclusion criteria: 1) Patients with STEMI within 12 h from symptom onset referred for primary angioplasty 2) age at least 18 years 3) chest pain lasting for at least 30 min associated with STsegment elevation of 0.2mV or more in at least two contiguous leads or new left bundle-branch block Exclusion criteria: 1) the concomitant detection of mechanical complications, 2) previous peritoneal or hemodialysis treatment, 3) the presence of postanoxic coma 4) pregnancy N total at baseline: Intervention 1: 145 Intervention 2: 154 Control 1: 142	Describe intervention (treatment/procedure/test): I1: sodium bicarbonate solution 1 ml/kg of body weight per hour for 12 h I2: 3 ml/kg of body weight per hour for 1 h, followed by 1 ml/kg of body weight per hour for 11 h	Describe control (treatment/procedure/test): C1: Intravenous normal saline (0.9%) at a rate of 1 ml/kg of body weight per hour for 12 h C2: normal saline at a rate of 3 ml/kg of body weight per hour for 1 h followed by 1 ml/kg of body weight per hour for 11 h	Length of follow-up: 3 days – laboratory parameters 12 months – clinical events Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): sCr increase ≥25% compared to baseline I1: 24 (16%) I2: 27 (18%) C1: 29 (19%) C2: 27 (19%) P=0.92 sCr increase ≥0.5 mg/dL from baseline I1: 5 (3%) I2: 3 (3%) C1: 7 (5%) C2: 8 (6%) P=0.51 Mortality did not differ at 30 days and at 12 months (data not shown).	Authors' conclusion In patients with STEMI undergoing PPCI, highvolume hydration with normal saline or sodium bicarbonate administrated at the time of contrast media administration was not associated with any significant advantage in terms of CI-AKI prevention.

		Control 2: 151 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I1: 64 ± 13* *I2: 65 ± 13* *C1: 65 ± 13* *C2: 65 ± 12* *Sex:* *I1: 72% M* *I2: 75% M* *C1: 75% M* *C2: 77% M* *eGFR ml/min* *I1: 80 ± 26* *I2: 82 ± 24* *C1: 81 ± 23* *C2: 82 ± 25* Groups comparable at baseline? Yes					
Ozcan, 2007	Type of study: randomized controlled trial Setting: elective patients Country: Turkey Source of	<u>Inclusion criteria</u>: patients who were scheduled for coronary angiography or percutaneous coronary intervention and had a baseline creatinine level N1.2 mg/dL	Describe intervention (treatment/procedure/test): 1.4% sodium bicarbonate Iv fluid (1 mL/kg/h, upper limit 100 mL/h) for 6 hours before and 6 hours after the procedure	Describe control (treatment/procedure/test): 0.9% saline Iv fluid (1 mL/kg/h, upper limit 100 mL/h) for 6 hours before and 6 hours after the procedure	<u>Length of follow-up</u>: 48 hours <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=an increase in serum creatinine N25% or 0.5 mg/dL after 48 hours) I: 12/88	Authors' conclusion Hydration with sodium bicarbonate provides better protection against CIN than the sodium chloride infusion does alone.

	funding: not reported	Exclusion criteria: 1) uncontrolled hypertension (systolic and diastolic blood pressure N160 mm Hg and N110 mm Hg, respectively), 2) emergency catheterization, 3) recent exposure to radiocontrast medium within 2 days, 4) volume overload, 5) serum creatinine levels >4 mg/dL N total at baseline: Intervention: 88 Control: 88 Important prognostic factors[2]: *For example* *age median (minimum – maximum)* *I: 68 (43-86)* *C: 70 (40-84)* *Sex:* *I: 73% M* *C: 75% M* *Creatinine clearance (mL/min)*				C: 4/88 P=0.043 RR (adjusted): 0.29 95% CI: 0.09 – 0.96	

		I: 53 (21 – 81) *C: 50 (22-101)* Groups comparable at baseline? Yes					
Ratcliffe, 2009	Type of study: randomized controlled trial Setting: elective patients, 1 center Country: United States of America Source of funding: not reported	<u>Inclusion criteria</u>: 1) ambulatory or hospitalized patients who were scheduled for invasive coronary angiography or percutaneous coronary intervention for the evaluation and treatment of coronary artery disease 2) willing to participate in the study, and were able to understand and provide informed written consent 3) patients older than 18 years of age, with renal insufficiency defined by elevated serum creatinine (greater than 132.6 µmol/L in men, and greater than 114.9 µmol/L	Describe intervention (treatment/procedure/test): Iv 0.9% NaHCO3 hydration at an infusion rate of 3 mL/kg/h for 1 h before contrast, and continued at 1 mL/kg/h during the procedure and for 6 h following contrast exposure	Describe control (treatment/procedure/test): Iv 0.9% saline hydration at an infusion rate of 3 mL/kg/h for 1 h before contrast, and continued at 1 mL/kg/h during the procedure and for 6 h following contrast exposure	<u>Length of follow-up</u>: 72 hours <u>Loss-to-follow-up</u>: Intervention: 15/30 (50%) Reasons: 11 lack of complete follow-up 4 other reasons Control: 10/29 (30%) 8 lack of complete follow-up 2 other reasons <u>Incomplete outcome data</u>: As above	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=an increase of greater than 25% in serum creatinine concentration from baseline to 72 h after administration of the contrast media) I: 2/19 (11%) C: 1/15 (7%) p>0.05	Authors' conclusion: CIN in high-risk patients may be effectively minimized solely through the use of an aggressive hydration protocol and an iso-osmolar contrast agent. The addition of NaHCO3 and/or NAC did not have an effect on the incidence of CIN.

		in women) or reduced calculated creatinine clearance (less than 1.002 mL/s) using the Cockcroft-Gault formula, and/or diabetes mellitus on oral antiglycemic or insulin therapy <u>Exclusion criteria</u>: 1) pregnancy or lactation; 2) acute myocardial infarction; 3) clinical signs of heart failure (or documented ejection fraction of less than 35%); 4) cardiogenic shock; 5) hypertrophic or restrictive cardiomyopathy; 6) contrast medium exposure within one week before the procedure; 7) previous serious reactions to contrast medium; 8) renal transplantation; dialysis; severe					

		comorbid illness; 9) use of dopamine, mannitol or fenoldopam; 10) newly discovered uncontrolled diabetes mellitus; 11) the inability to obtain informed consent or follow-up <u>N total at baseline</u>: Intervention: Control: <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 67 ± 11* *C: 64 ± 10* *Sex:* *I: 58% M* *C: 60% M* Groups comparable at baseline? Yes					
Recio-Mayoral, 2007	Type of study: randomized controlled trial Setting: emergency patients, one hospital	<u>Inclusion criteria</u>: 1) acute coronary syndrome (ACS) patients who were admitted to our coronary care unit 2) patients with myocardial	Describe intervention (treatment/procedure/test): Active prophylactic treatment of PCI: Intravenous bolus of 5 ml/kg/h of alkaline saline solution with 154	Describe control (treatment/procedure/test): Standard treatment: perfusion of isotonic saline (0.9%) at rate of 1 ml/kg/h for 12 h after PCI plus 2 doses of 600 mg N-AC	<u>Length of follow-up</u>: 3 days <u>Loss-to-follow-up</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=an absolute	Authors' conclusion: Rapid intravenous hydration with sodium bicarbonate plus N-AC before

	Country: United Kingdom Source of funding: not reported	infarction treated with primary PCI or rescue PCI, as well as patients with high-risk non–ST-segment elevation ACS needing urgent revascularization <u>Exclusion criteria</u>: 1) end-stage renal failure on dialysis, 2) uncontrolled hypertension (systolic blood pressure >160 mm Hg and/or diastolic blood pressure >100 mm Hg) 3) signs of cardiac failure not responding to medical treatment, 4) known severe aortic valve stenosis (area >1.0 cm2), 5) allergy to iodated contrast or NAC 6) pregnancy <u>N total at baseline</u>: Intervention: 56 Control: 55 <u>Important prognostic factors</u>[2]:	mEq/l of sodium bicarbonate in 5% glucose and H2O (adding 77 ml of 1,000 mEq/l sodium bicarbonate to 433 ml of 5% glucose in H2O) plus 2,400 mg of N-AC in the same solution over 1 hour the bolus was administered in the 60 min preceding contrast injection Afterward, patients received fluid therapy, without N-AC, at 1.5 ml/kg/h perfusion rate in the 12 h after the procedure plus 2 doses of 600 mg N-AC orally the next day	orally the next day	<u>Incomplete outcome data</u>: Not reported	increase in SCr concentration of 0.5 mg/dl or more from baseline value in the 3 days after PCI) I: 1/55 (2%) C: 12/55 (22%) Odds ratio: 0.065 (95% CI: 0.008 – 0.521, p=0.01) Acute anuric renal failure I: 1/55 (2%) C: 7/55 (13%) P=0.032	contrast injection is effective and safe in the prevention of CIN in patients undergoing emergency PCI.

		For example *age ± SD:* *I: 65 ± 10* *C: 64 ± 9* *Sex:* *I: 68% M* *C: 71% M* *Glomerular filtration rate (mL/min)* *I: 75 ± 21* *C: 74 ± 20* Groups comparable at baseline? Yes					
Sodium bicarbonate short schedule versus saline long schedule for coronary angiography and/or percutaneous intervention							
Briguori, 2007	Type of study: randomized controlled trial Setting: elective patients, one hospital Country: Italy Source of funding: not reported	<u>Inclusion criteria</u>: 1) patients with chronic kidney disease who underwent coronary and/or peripheral angiography and/or angioplasty 2) _18 years of age 3) stable serum creatinine concentration >2.0 mg/dL and/or or an estimated glomerular filtration rate <40 mL/ min/1.73 m^2	Describe intervention (treatment/procedure/test): 154 mEq/L sodium bicarbonate in dextrose and $H2O$,. The initial intravenous bolus was 3 mL/kg/h for 1 hour immediately before contrast injection. After this, patients received the same fluid at a rate of 1 mL/kg/h during contrast exposure and for 6 hours after the procedure. NAC orally at a dose of 1200 mg twice daily on the day before and the day of administration of the contrast agent (total of 2 days).	Describe control (treatment/procedure/test): Isotonic saline (0.90%) was given intravenously at a rate of 1 mL/kg body weight per hour (0.5 mL/kg for patients with left ventricular ejection fraction _40%) for 12 hours before and 12 hours after administration of the contrast agent. NAC orally at a dose of 1200 mg twice daily on the day before and the day of administration of the contrast agent (total of 2 days).	<u>Length of follow-up</u>: 48 hours for laboratory parameters 5 days for clnical events <u>Loss-to-follow-up</u>: Intervention: 9/117 (8%) 8 had no follow-up sCr value 1 had no contrast exposure	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=increase _25% of creatinine concentration) I: 2/108 (2%) C: 11/111 (10%) P=0.02 Renal failure requiring temporary dialysis: I: 1/108 (1%) C: 1/111 (1%)	Authors' conclusion: The strategy of volume supplementation by sodium bicarbonate plus NAC seems to be superior to the combination of normal saline with NAC alone or with the addition of ascorbic acid in preventing CIN in patients at medium to high risk.

		Exclusion criteria: 1) serum creatinine levels >8 mg/dL, 2) a history of dialysis, 3) multiple myeloma, 4) pulmonary edema, 4) acute myocardial infarction, 5) recent exposure to radiographic contrast within 2 days of the study, 6) pregnancy, 7) administration of theophylline, dopamine, mannitol, or fenoldopam N total at baseline: Intervention: 111 Control: 108 Important prognostic factors[2]: *For example* *age ± SD:* *I: 70 ± 9* *C: 71 ± 9* *Sex:* *I: 88% M* *C: 81% M* Groups comparable			Control: 7/118(6%) 7 had no follow-up sCr value Incomplete outcome data: As above	p-value not reported	

		at baseline? Yes					
Castini, 2008	Type of study: randomized controlled trial Setting: one hospital Country: Italy Source of funding: not reported	<u>Inclusion criteria</u>: 1) patients undergoing coronary angiography and/or percutaneous coronary intervention 2) aged 18 years or older with stable serum creatinine levels ≥1.2 mg/dL <u>Exclusion criteria</u>: 1) serum creatinine levels >4 mg/dL, 2) a history of dialysis, 3) multiple myeloma, 4) pulmonary edema, 5) cardiogenic shock, 6) acute myocardial infarction, 7) emergency catheterization, 8) recent exposure to radiographic contrast media within 7 days of the study, 9) allergy to iodinate contrast media or NAC,	Describe intervention (treatment/procedure/test): 154 mL of 1000 mEq/L SB added to 846 mL of 5% dextrose in H2O. The initial intravenous bolus was 3 mL/kg for 1 hour immediately before contrast injection. Thereafter, patients received the same fluid at a rate of 1 mL/kg per hour during contrast exposure and for 6 hours after the procedure.	Describe control (treatment/procedure/test): saline (0.9%) given intravenously at a rate of 1 mL/kg body weight per hour for 12 hours before and 12 hours after administration of the contrast agent	<u>Length of follow-up</u>: 5 days <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN1 (=an increase in serum creatinine concentration≥25% over the baseline value in any of the 3 predefined time-points: 24 hours, 48 hours and 5 days) I: 7 (14%) C: 7 (14%) P>0.05 CIN2 (=the rate of an absolute increase in serum creatinine concentration ≥0.5 mg/dL at the same time-points) I: 6 (12%) C: 4 (8%) p>0.05 No patients required dialysis.	Authors' conclusion: Our findings suggest that neither the addition of NAC nor the administration of SB add further benefit in CIN prevention, compared to standard hydration with isotonic saline infusion.

		10) previous enrollment in the same or other protocols, 11) pregnancy, 12) administration of theophylline, mannitol, dopamine, dobutamine, nonsteroidal anti-inflammatory drugs, or fenoldopam. <u>N total at baseline</u>: Intervention: 52 Control: 51 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 70 ± 8* *C: 73 ± 8* *Sex:* *I: 85% M* *C: 84% M* Groups comparable at baseline? Yes					
Hafiz, 2012	Type of study: randomized controlled trial Setting:	<u>Inclusion criteria</u>: 1) patients undergoing elective coronary and peripheral	Describe intervention (treatment/procedure/test): dextrose 5% in water containing 154 mEq/L of NaHCO3 with or	Describe control (treatment/procedure/test): intravenous 0.9% normal saline with or without NAC	<u>Length of follow-up</u>: 48 hours <u>Loss-to-</u>	Outcome measures and effect size (include 95%CI and p-value if available):	Authors' coclusion: Incidence of CI-AKI was no

	elective patients, two tertiary hospitals Country: United states of america Source of funding: not reported	angiography and intervention. 2) serum creatinine >1.6 mg/dl in non-diabetics and >1.4 mg/dl in diabetics or an estimated glomerular filtration rate (eGFR) of <50 ml/min/1.73 m2, calculated by the Modification of Diet in Renal Disease (MDRD) formula 3) age >18 years <u>Exclusion criteria</u>: (1) were on dialysis; (2) had unstable renal function (defined as change in serum creatinine of >0.4 mg/dl within 48 hr prior to the index procedure), (3) had pulmonary edema, (4) had serum bicarbonate level >34 mmol/L; (5) received fenoldapam, mannitol, dopamine, or NAC within 48 hr prior to	without NAC NAC was used in 50% of patients in both study arms in a similarly randomized fashion as above; 1,200 mg was administered orally 2–12 hr before the procedure followed by another 1,200 mg oral dose 6–12 hr after the procedure	NAC was used in 50% of patients in both study arms in a similarly randomized fashion as above; 1,200 mg was administered orally 2–12 hr before the procedure followed by another 1,200 mg oral dose 6–12 hr after the procedure	<u>follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	CI-AKI (=increase in serum creatinine concentration of either >25% or >0.5 mg/dl at 48 hr after the procedure) I: 12% C: 9% p>0.05 There were no deaths or major adverse effects noted in our patient population during the study period.	different in the NaHCO3 group compared to saline group, and NAC did not reduce CI-AKI in the two study arms.

		the index procedure; (6) were in cardiogenic shock, (7) were allergic to contrast media, (8) were pregnant, (9) were unable to provide informed consent. N total at baseline: Intervention: 159 Control: 161 Important prognostic factors[2]: *For example* *age (IQR):* *I: 74 (65-80)* *C: 73 (63-80)* *Sex:* *I: 56% M* *C: 57% M* *eGFR* *I: 42 (32-51)* *C: 41 (33-50)* Groups comparable at baseline? Yes					
Klima, 2012	Type of study: randomized controlled trial Setting:	Inclusion criteria: All patients admitted with renal dysfunction {actual serum creatinine	Describe intervention (treatment/procedure/test): The initial intravenous bolus was 3 mL/kg/h of 166 mEq/L sodium	Describe control (treatment/procedure/test): The infusion of 0.9% sodium chloride was administered at a	Length of follow-up: 48 hours Loss-to-	Outcome measures and effect size (include 95%CI and p-value if available):	Authors' conclusion: Volume supplementation

	elective patients, multi-center trial Country: Switzerland Source of funding: commercial and non-commerzial	level above the upper limit of normal of the serum creatinine (0.93 mmol/L for women and .117 mmol/L for men) or estimated glomerular filtration rate (eGFR) ,60 mL/min/1.73 m2 [eGFR calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation16]} scheduled to undergo an intra-arterial or intravenous radiographic contrast procedure on the next day <u>Exclusion criteria</u>: 1) age ≥18 years, 2) pre-existing dialysis, allergy to radiographic contrast, 3) pregnancy, 4) severe heart failure (NYHA functional class III	bicarbonate for 1 h immediately before radiocontrast injection. Following this, patients received the same fluid at a rate of 1 mL/kg/h during the contrast exposure and for 6 h after the procedure.	continuous rate of 1 mL/kg/h, beginning from 8 p.m. on the day before the procedure and for at least 12h after the procedure.	<u>follow-up</u>: Intervention: 6/93 (6%) 5 received no radiocontrast 1 refused participation Control: 4/93 (4%) 4 received no radiocontrast <u>Incomplete outcome data</u>: As above	CIN (=an increase of ≥25% or an increase of ≥44 µmol/L in the baseline serum creatinine concentration within 48 h) I: 9% C:1% P=0.02 No patient experienced a serious adverse event related to the infusion (death, intensive care unit admission). Also, no patient required intravenous diuretics or nitrates due to pulmonary congestion.	with 24 h sodium chloride 0.9% is superior to sodium bicarbonate for the prevention of CIN.

		and IV), 5) N-acetylcysteine ≤24 h before contrast, 6) clinical condition requiring continuous fluid therapy, e.g. severe sepsis <u>N total at baseline</u>: Intervention: 87 Control: 89 <u>Important prognostic factors</u>[2]: *For example* *age median (IQR):* *I: 78 (70-82)* *C: 75 (70-82)* *Sex:* *I: 66% M* *C: 62% M* *eGFR ± SD* *I: 43 ± 11* *C: 43 ± 12* Groups comparable at baseline? Yes					
Lee, 2011	Type of study: randomized controlled trial Setting: elective	<u>Inclusion criteria</u>: 1) patients undergoing coronary or endovascular angiography or	Describe intervention (treatment/procedure/test): Sodium bicarbonate infusion (154 mEq/L in dextrose and water) was	Describe control (treatment/procedure/test): 0.9% sodium chloride 1 ml/kg/hour for 12 hours before and after the	<u>Length of follow-up</u>: 48 hours for laboratory parameters 6 months for	Outcome measures and effect size (include 95%CI and p-value if available):	Authors' conclusion: In conclusion, hydration with sodium

	patients, multicentre trial academic hospitals Country: Korea Source of funding: not reported	intervention 2) serum creatinine ≥1.1 mg/dl, estimated glomerular filtration rate (eGFR) ≤60 ml/min/1.73 m^2, 3) age ≥18 years, 4) diagnosis with diabetes mellitus <u>Exclusion criteria</u>: 1) inability to obtain informed consent, 2) serum creatinine ≥8 mg/dl, eGFR ≤15 ml/min/1.73 m^2 at rest, end-stage renal disease on hemodialysis, 3) multiple myeloma, 4) pulmonary edema, 5) uncontrolled hypertension (systolic pressure >160 mm Hg or diastolic pressure >100 mm Hg), 6) acute ST-segment elevation myocardial infarction while	begun 1 hour before the start of contrast injection, starting at 3 ml/kg/hour and decreasing to 1 ml/ kg/hour during the procedure and for 6 hours after completion of the procedure All patients received NAC 1,200 mg 2 times/day for 2 days starting the day before the index procedure	procedure All patients received NAC 1,200 mg 2 times/day for 2 days starting the day before the index procedure	clinical parameters <u>Loss-to-follow-up</u>: Intervention: 5/193 (3%) All had no laboratory data Control: 2/189 (1%) All had no laboratory data <u>Incomplete outcome data</u>: As above	CIN (=a ≥25% increase in serum creatinine concentration or a ≥0.5 mg/dl absolute increase in serum creatinine from baseline within 48 hours after contrast exposure) I: 17 (9%) C: 10 (5%) P=0.17 Requirement of hemodialysis I: 4 (2%) C: 2 (1%) P=0.69 Rates of death, myocardial infarction, and stroke did not differ significantly at 1 month and 6 months after contrast exposure.	bicarbonate is not superior to hydration with sodium chloride in preventing CIN in patients with diabetic nephropathy undergoing coronary or endovascular angiography or intervention. Infusion rates were decreased to 0.5 ml/kg/hour in patients with left ventricular ejection fraction ≤45% in the 2 treatment arms.

		undergoing primary percutaneous intervention, 7) emergency coronary angioplasty or angiography, 8) use of contrast media within the previous 2 days, 9) pregnancy, 10) allergy to contrast medium 11) medications such as theophylline, dopamine, mannitol, fenoldopam, and NAC <u>N total at baseline</u>: Intervention: 193 Control: 189 <u>Important prognostic factors</u>[2]: *For example* *age median (IQR)* *I: 69 (63-73)* *C: 68 (67-72)* *Sex:* *I: 70% M* *C: 71% M* *eGFR:*					

		I: 46 (34-53) *C: 46 (37-53)* Groups comparable at baseline? Yes					
Maioli, 2008	Type of study: randomized controlled trial Setting: elective patients, one center Country: Italy Source of funding: not reported	<u>Inclusion criteria</u>: 1) patients with pre-angiographic estimated creatinin clearance <60 ml/min 2) undergoing planned angiographic procedures <u>Exclusion criteria</u>: 1) creatinine clearance ≥ 60 ml/min n = 691 2) refusal to participate n = 18 3) administration of contrast medium within the previous 10 days n = 12 4) end stage renal disease n = 3 <u>N total at baseline</u>: Intervention: 250 Control: 252 <u>Important prognostic factors</u>[2]: *For example age median (IQR):*	Describe intervention (treatment/procedure/test): Sodium bicarbonate (154 mEq/l in dextrose and water) received 3 ml/kg for 1 h before contrast medium, followed by an infusion of 1 ml/kg/h for 6 h after the procedure. All patients received 600 mg oral NAC twice a day from the day before to the day after the procedure	Describe control (treatment/procedure/test): 1 ml/kg/h 0.9% sodium chloride for 12 h before and after the procedure	<u>Length of follow-up</u>: 5 days <u>Loss-to-follow-up</u>: Intervention: 4/252 (2%) 3 died 1 acute renal failure Control: 5/250 (2%) 4 died 1 acute renal failure <u>Incomplete outcome data</u>: As above	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=an absolute increase of at least 0.5 mg/dl over baseline serum creatinine within 5 days after the administration of the contrast medium) I: 25 (10%) C: 29 (12%) P=0.60 CIN2 (=as a relative increase _25% over baseline serum creatinine within 5 days after contrast agent administration) I: 15% C: 21% P=0.13	Authors' conclusion: Hydration with sodium bicarbonate plus NAC before contrast medium exposure is not more effective than hydration with isotonic saline plus NAC for prophylaxis of CIN in patients with moderate-to-severe renal dysfunction.

		I: 74 (67-79) *C: 74 (70-79)* *Sex:* *I: 57% M* *C: 61% M* *eGFR ± SD:* *I: 43 ± 11* *C: 42 ± 10* Groups comparable at baseline? Yes				Death and acute renal failure, see column "Follow-up" for numbers, no significant difference in clinical events.	
Nieto-Rios, 2014	Type of study: randomized controlled trial Setting: elective patients, single center Country: Colombia Source of funding: not reported	<u>Inclusion criteria</u>: 1) Inpatients in a tertiary center, scheduled to undergo a procedure with the nonionic radiographic contrast agent iohexol. 2) serum creatinine levels of at least 1.2 mg/dL (106.1 µmol/L) and/or type 2 diabetics, <u>Exclusion criteria</u>: 1) current clinical diagnosis of exacerbated congestive heart failure, 2) ejection fraction <35% by previous	Describe intervention (treatment/procedure/test): 3 ml/kg of sodium bicarbonate solution (150 mEq/L) one hour prior to procedure and then drip rate was decreased to 1 ml/ kg/hour until 6 hours post procedure	Describe control (treatment/procedure/test): 1 ml/ kg/hour of normal saline solution, starting 12 hours before and continuing 12 hours after iohexol contrast	<u>Length of follow-up</u>: 5 days <u>Loss-to-follow-up</u>: Intervention: 7/107 (7%) 3 died 1 withdrawed 3 technical difficulties Control: 1/113 (1%) 1 died <u>Incomplete outcome data</u>: As above	Outcome measures and effect size (include 95%CI and p-value if available): CIN (= increase in serum creatinine on 25% or more within 2 days after administration of radiographic con-trast) I: 12 (12%) C: 8 (7%) RR: 1.68, 95% CI: 0.72 – 3.94 p>0.05 Decompensated heart failure I: 3 (3%) C: 7 (6%)	Authors conclusion: Our investigation showed that there were no differences between normal saline solution (extended infusion) *vs.* bicarbonate solution for nephroprotection.

		echocardiography, 3) signs of acute pulmonary edema within 48 hours before the procedure, 4) systolic blood pressure <90 mmHg or requirement of vasopressors support, 5) patients with exposure to contrast 30 days prior to the study, 6) known allergy to contrast dye, 7) chronic renal disease with dialysis therapy, 8) criteria for dialytic urgency, 9) pregnancy, 10) requirement of an emergency procedure (e.g., aortography for diagnosis of aortic aneurism), 11) patients with serum potassium <3 mEq/L (because of the risk of hypokalemia induced by bicarbonate), 12) uncompensated				P=0.34	

		diabetes mellitus (four different values >200 mg/dL in the previous 24 hours) 13) patient or physician refusal to participate. <u>N total at baseline</u>: Intervention: 107 Control: 113 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 61 ± 17* *C: 60 ± 17* *Sex:* *I: 57% M* *C: 58% M* *Baseline sCr (mg/dL):* *I: 1.3 ± 0.3* *C: 1.3 ± 0.3* Groups comparable at baseline? Yes					
Shavit, 2009	Type of study: randomized controlled trial Setting: elective	<u>Inclusion criteria</u>: 1) patients with chronic kidney disease (CKD) stage III–IV undergoing cardiac	Describe intervention (treatment/procedure/test): 154 mEq/L sodium bicarbonate in 5% dextrose in water mixed by adding 154 mL of 1,000 mEq/L	Describe control (treatment/procedure/test): 12-hour infusion of 154 mEq/L (0.9%) sodium chloride at a rate of 1 mL/kg per hour before cardiac	<u>Length of follow-up</u>: 2 days <u>Loss-to-follow-up</u>:	Outcome measures and effect size (include 95%CI and p-value if available):	Authors' conclusion: Hydration with sodium bicarbonate is not

	patiens, single-center Country: Israel Source of funding: not reported	catheterization <u>Exclusion criteria</u>: 1) plasma creatinine levels more than 8 mg/dL or eGFR less than 15 mL/min, change in plasma creatinine levels of ≥0.5 mg/dL during the previous 24 hours, 2) preexisting dialysis, multiple myeloma, 3) pulmonary edema, 4) uncontrolled hypertension (systolic >160 mmHg, diastolic >100 mmHg), 5) recent exposure to radiographic contrast, or other nephrotoxic medications (within 2 days of the study), 6) allergy to radiocontrast, 7) pregnancy <u>N total at baseline</u>: Intervention: 51	sodium bicarbonate to 846 mL of 5% dextrose in water. The initial IV bolus was 3 mL/kg for 1 hour before cardiac catheterization. Following this bolus, patients received the same fluid at a rate of 1 mL/kg per hour during the contrast exposure and for 6 hours after the procedure. For patients weighing more than 110 kg, the initial fluid bolus and drip were limited to those doses administered to patients weighing 110 kg.	catheterization and NAC 600 mg × 2/d orally the day before and the day of the procedure	Intervention: 0 (0%) Control: 5/41 (12%) No laboratory evaluation at baseline or after contrast exposure <u>Incomplete outcome data</u>: As above	CI-AKI (=an increase of 25% or 0.3 mg/dL or more in plasma creatinine within 2 days of contrast administration) I: 5/51 (10%) C: 3/36 (8%) p>0.05 CI-AKI2 (=an increase in plasma creatinine of 0.3 mg/dL or more from baseline) I: 17% C: 16% P>0.05 No patient developed more than 50% increment of creatinine or required renal replacement therapy during the hospitalization.	more effective than hydration with sodium chloride and oral NAC for prophylaxis of CI-AKI in patients with CKD stage III–IV undergoing cardiac catheterization.

		Control: 36 <u>Important prognostic factors[2]</u>: For example *age ± SD:* *I: 72 ± 10* *C: 71 ± 9* *Sex:* *I: 84% M* *C: 70% M* *eGFR (ml/min/1.73m^2) ± SD:* *I: 43 ± 11* *C: 40 ± 10* Groups comparable at baseline? Yes					
Sodium bicarbonate versus saline: "other schedules" for coronary angiography and/or percutaneous intervention							
Chong, 2015	Type of study: randomized controlled trial Setting: University Heart Centre Country: Singapore Source of funding: not reported	Inclusion criteria: 1) adults >21 years of age; 2) glomerular filtration rate (GFR) of 15–60 mL/min/1.73m2 – calculated by the abbreviated Modification of Diet in Renal Disease (MDRD) formula – 3) scheduled to undergo elective	Describe intervention (treatment/procedure/test): I1: High-dose oral NAC with a sustained intravenous sodium chloride infusion (NAC group) I2: Intravenous sodium bicarbonate infusion (SOB group)	Describe control (treatment/procedure/test): C1: Oral NAC and abbreviated intravenous sodium bicarbonate infusion (COM group)	<u>Length of follow-up</u>: 48 hrs <u>Loss-to-follow-up</u>: I1: 28/185 I2: 29/182 C1: 25/181 Death: I1: 0/185 I2: 1/182 C1: 2/181	Outcome measures and effect size (include 95%CI and p-value if available): CIN, which was defined as ≥25% increase of serum Cr concentration or a ≥44 µmol/L (0.5mg/dL) increase in serum Cr within 48 h of cardiac	Authors' conclusion *'The combination regimenwas not superior to individual regimens in preventing CIN in patientswith baseline renal impairment. There was a trend suggesting that the 12-hour*

		cardiac catheterisation with or without PCI 4) were able to receive pre-hydration for 12 h. <u>Exclusion criteria:</u> 1) end-stage renal failure with GFR of b15 mL/min/1.73 m2, acute renal failure with a N44 μmol/L increase in serum Cr levels in the previous 24 h; 2) pre-existing dialysis; 3) pulmonary oedema or moderate to severe congestive heart failure (New York Heart Association III–IV); 4) inability to withstand the fluid load; 5) presence of haemodynamic compromise, uncontrolled hypertension (untreated systolic blood pressure N160mmHg, or				catheterisation or PCI I1: 6.5% I2: 12.8% C1: 10.6% P=0.214	*sustained sodium chloride prehydration regimen was more protective than the 1-hour abbreviated SOB regimen.'*

		diastolic blood pressure N100mmHg) 6) emergency cardiac catheterisation 7) exposure to contrast in the previous two days; 8) allergies to contrast or NAC; 9) administration of sodium bicarbonate or NAC within 48 h of cardiac catheterisation; 10) clinical conditions requiring continuous fluid therapy such as severe sepsis; 11) Use of potentially renal-toxic drugs; 12) cisplatin within 48 h of cardiac catheterisation and throughout the study duration; <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 69 ± 10* *I2: 71 ± 10*					

		C: 67 ± 10 *Sex:* *I1: 72% M* *I2: 78% M* *C: 78% M* Groups comparable at baseline? Yes					
Motohiro, 2011	Type of study: randomized controlled trial Setting: elective patient, 2 hospitals Country: Japan Source of funding: not reported	<u>Inclusion criteria</u>: 1) patients undergoing coronary angiography or intervention 2) ≥20 years old 3) had an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 <u>Exclusion criteria</u>: 1) serum creatinine levels >4 mg/dl, 2) changes in serum creatinine levels of ≥0.5 mg/dl during the previous 24 hours, 3) pre-existing dialysis, 4) pulmonary edema, 5) uncontrolled hypertension (treated systolic	Describe intervention (treatment/procedure/test): 0.9% sodium chloride for 12 hours before and after the procedure. Sodium bicarbonate solution was prepared by adding 154 ml of sodium bicarbonate 1,000 mEq/L to 846 ml of 5% dextrose in water. In the sodium bicarbonate group the sodium bicarbonate solution was changed 3 hours before contrast administration	Describe control (treatment/procedure/test): 0.9% sodium chloride for 12 hours before and after the procedure.	<u>Length of follow-up</u>: 1 months <u>Loss-to-follow-up</u>: Intervention: 2/79 (2%) No laboratory test results Control: 1/79 (1%) Angialgia due to sodium bicarbonate infusion <u>Incomplete outcome data</u>: As above	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=25% increase or an absolute increase of _0.5 mg/dl in serum creatinine from baseline value, which appeared within 2 days of the produce) I: 2 (3%) C: 10 (13%) P=0.02 relative risk 0.176, 95% confidence interval 0.037 to 0.83 No patient required Hemodialysis.	Authors' conclusion Sodium chloride plus sodium bicarbonate is more effective than sodium chloride alone for prophylaxis of CIN and can lead to retention of better long-term renal function.

		blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg), 6) emergency catheterization, 7) exposure to radiographic contrast within previous 2 days, 8) any allergy to radiographic contrast medium <u>N total at baseline</u>: Intervention: 77 Control: 78 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 74 ± 7* *C: 71 ± 9* *Sex:* *I: 64% M* *C: 76% M* Groups comparable at baseline? Yes					
Tamura, 2009	Type of study: randomized controlled trial	<u>Inclusion criteria</u>: 1) Patients who were scheduled for elective coronary	Describe intervention (treatment/procedure/test): Standard hydration with sodium	Describe control (treatment/procedure/test): Standard hydration with sodium	<u>Length of follow-up</u>: 3 days	Outcome measures and effect size (include 95%CI and p-value if	Authors' conclusion In conclusion,

	Setting: elective patients, two hospitals Country: Japan Source of funding: not reported	arteriography or percutaneous coronary intervention 2) age >20 years 3) serum creatinine (Cr) level >1.1 to <2.0 mg/dl. <u>Exclusion criteria</u>: 1) allergy to contrast medium, pregnancy, 2) history of dialysis, 3) exposure to contrast-medium within the preceding 48 hours of the study, 4) acute coronary syndrome within the preceding 1 month of the study, 5) severe symptoms of heart failure (New York Heart Association functional class IV), 6) left ventricular ejection fraction >25%, 7) severe chronic respiratory disease, 8) single functioning kidney, 9) administration of	chloride plus single-bolus intravenous administration of sodium bicarbonate (20 ml /20 mEq; Meyron 84, Otsuka Pharmaceutical, Inc., Tokyo, Japan) 5 minutes before contrast exposure	chloride alone (=intravenous administration with isotonic saline (0.9%) at a rate of 1 ml/kg/hour (0.5 ml/kg/hour for patients with left ventricular ejection fraction <40%) for 12 hours before and 12 hours after an elective coronary procedure. For patients weighing >80 kg, infusion rate was limited to 80 ml/hour (40 ml/hour for patients with left ventricular ejection fraction _40%).	<u>Loss-to-follow-up</u>: All patients completed the study <u>Incomplete outcome data</u>: All patients completed the study	available): CIN (=an increase ≥25% or ≥0.5 mg/dl in serum Cr within the first 3 days after the procedure compared to baseline value) I: 1.4% C: 12.5% P=0.017 Adverse clinical events (acute pulmonary edema, acute renal failure requiring dialysis, and death within 7 days of procedure) I: 0% C: 1.4% p>0.05	single-bolus intravenous administration of sodium bicarbonate in addition to standard hydration can more effectively prevent CIN than standard hydration alone in patients with mild renal insufficiency undergoing an elective coronary procedure.

		N-acetylcysteine, theophylline, dopamine, or mannitol <u>N total at baseline</u>: Intervention: 72 Control: 72 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 73 ± 8* *C: 72 ± 10* *Sex:* *I: 83% M* *C: 92% M* Groups comparable at baseline? Yes					
Turedi, 2016	Type of study: randomized controlled trial Setting: academic emergency center Country: Turkey Source of funding: not reported	<u>Inclusion criteria:</u> 1) Undergoing contrastenhanced thoracic CT due to suspected PE; 2) aged over 18 years; 3) with measure-able basal creatinine levels pretomography and; 4) measureable serum creatinine levels 48– 72 hours	Describe intervention (treatment/procedure/test): I1: 3 mL/kg intavenous NAC+NS solution (3 g NAC was made up to 1000 mL with NS), I2: NaHCO3 + NS solution (132 mEq NaHCO3 was made up to 1000 mL with NS)	Describe control (treatment/procedure/test): C1: NS alone 1 hour before CTPA and 1 mL/kg intavenous per hour for a minimum of 6 hour after CTPA.	<u>Length of follow-up</u>: 48-72 hrs <u>Loss-to-follow-up</u>: I1: 7/85 I2: 8/85 C1: 11/87 Death: I1: 4/85 I2: 2/85 C1: 6/87	Outcome measures and effect size (include 95%CI and p-value if available): CIN development creatinine levels and post-CTPA creatinine levels measured 48–72 hours following contrast exposure and an increase	Authors' conclusion *'In conclusion, there were no statistically significant differences observed among prophylactic NAC, NaHCO3, and NS in prevention of CIN following contrast-enhanced*

		posttomography, and with one or more of the risk factors for CIN. The risk factors were preexisting renal dysfunction (Cr 1.4 mg/dL or a high or calculated glomerular filtration rate [GFR] < 60 mL/min/1.73 m^2), diabetes mellitus, hypertension receiving treatment, hypotension (systolic blood pressure < 90 mm Hg), coronary artery disease, history of nephrotoxic drug use (nonsteroidal anti-inflammatory drugs, cisplatin, aminoglycoside, amphotericin B), liver disease, congestive heart failure (active or history thereof), age 75 or over, and anemia (hematocrit < 30%).				≥25% or 0.5 mg/dL I1: 23.5% I2: 21.2% C1: 26.4% P=0.719	*CTPA.'*

		Exclusion criteria: 1) end-stage renal disease already in peritoneal dialysis; 2) hemodialysis; 3) pregnant women; 4) subjects with a known allergy to NAC or NaHCO3; 5) patients requiring NAC therapy or NaHCO3 therapy for existing additional disease; 6) exposed to contrast material for any reason in the previous 10 days or 7) during the in-hospital follow-up period 8) patients who refused to participate <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 76 (72-80)* *I2: 77 (71-80)* *C: 74 (73-76)* *Sex:*					

		I1: 48% M *I2: 51% M* *C: 53% M* Groups comparable at baseline? Yes					
Ueda, 2011	Type of study: randomized controlled trial Setting: emergency patients, single center Country: Japan Source of funding: not reported	Inclusion criteria: 1) patients undergoing an emergent (within 60 minutes of admission) diagnostic or interventional coronary procedure, such as coronary angiography or percutaneous coronary intervention 2) >20 years old 3) had renal insufficiency, defined by a serum creatinine (Cr) concentration of >1.1 mg/dl or estimated glomerual filtration rate (eGFR) of <60 ml/min Exclusion criteria: 1) change in the serum Cr concentration of	Describe intervention (treatment/procedure/test): Intravenous bolus injection of 154 mEq/L of sodium bicarbonate at a dose of 0.5 ml/kg, as soon as possible after they were admitted, before the administration of the contrast medium Intravenous infusion of 154 mEq/L sodium bicarbonate at 1 ml/kg/hour during and for 6 hours after the coronary procedure	Describe control (treatment/procedure/test): Intravenous bolus injection of 154 mEq/L of sodium chloride at a dose of 0.5 ml/kg, as soon as possible after they were admitted, before the administration of the contrast medium Intravenous infusion of 154 mEq/L sodium bicarbonate at 1 ml/kg/hour during and for 6 hours after the coronary procedure	Length of follow-up: 2 days Loss-to-follow-up: Intervention: 0 (0%) Control: 1/30 (3%) Circulatory failure Incomplete outcome data: As above	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=an increase by >25% or >0.5 mg/dl of the serum creatinine level within 2 days after the procedure) I: 1 (3%) C: 8 (28%) RR: 0.12, 95% CI: 0.016 – 0.91 P=0.01 Congestive heart failure I: 5/30 (17%) C: 6/29 (21%) p>0.05 Death I: 2/30 (7%) C: 2/29 (7%) p>0.05 No patients	Authors' conclusion In conclusion, rapid alkalization by bolus injection of sodium bicarbonate was effective for the prevention of CIN in patients with CKD undergoing emergent procedures.

		>0.5 mg/dl during the 24 hours before the procedure, 2) pre-existing dialysis, exposure to the contrast media within 2 days before the study, 3) allergy to the contrast media, pregnancy, 4) previous or planned administration of mannitol, fenoldopam, *N*-acetylcysteine, theophylline, dopamine, or nonstudy sodium bicarbonate <u>N total at baseline</u>: Intervention: 30 Control: 29 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 77 ± 9* *C: 75 ± 10* *Sex:* *I: 79% M* *C: 77% M*				developed acute renal failure requiring hemodialysis.	

		sCr (mg/dL) ± SD: *I: 1.32 ± 0.46* *C: 1.51 ± 0.59* Groups comparable at baseline? Yes					
Sodium bicarbonate short schedule versus saline long schedule for computed tomography							
Kooiman, 2014	Type of study: randomized controlled trial Setting: elective patients, multi-center trial Country: the Netherlands Source of funding: non-commercial	<u>Inclusion criteria</u>: 1) In- and outpatients electively scheduled for CE-CT regardless of the indication 2) least 18 years of age, had CKD (eGFR <60 mL/min/1.73 m^2 estimated by the Modification of Diet in Renal Disease formula 3) eligible for the fluid challenge of saline hydration <u>Exclusion criteria</u>: 1) pregnancy, 2) previous contrast administration within the last 7 days, 3) documented allergy for iodinated contrast media, 4) haemodynamic instability (systolic	Describe intervention (treatment/procedure/test): 250 mL intravenous 1.4% sodium bicarbonate 1 h prior to CE-CT without hydration post-CE-CT	Describe control (treatment/procedure/test): 2000 mL of intravenous 0.9% saline, 1000 mL prior to and 1000 mL post-CE-CT	<u>Length of follow-up</u>: 96 hours <u>Loss-to-follow-up</u>: Intervention: 15/267(6%) 2 treated according to protocol 5 CT without iv contrast 6 CT cancelled and no hydration Control: 20/281 (7%) 7 treated according to protocol 7 CT cancelled and no hydration 4 CT without iv contrast 2 treated with sodium bicarbonate	Outcome measures and effect size (include 95%CI and p-value if available): CI-AKI (=serum creatinine increase >25%/>44 µmol/L (0.5 mg/dL) I: 8 (3%) C: 14 (5%) P=0.23 Recovery of kidney function: I: 75% C: 69% P=0.81 Acute heart failure due to volume expansion (based on the treating physician's clinical judgement) occurred in none of the patients in the sodium bicarbonate group	Authors' conclusion Short hydration with sodium bicarbonate prior to CE-CT was non-inferior to peri-procedural saline hydration with respect to renal safety and may result in healthcare savings.

		blood pressure <100 mmHg) 5) previous participation in the trial <u>N total at baseline</u>: Intervention: 267 Control: 281 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 72 ± 10* *C: 73 ± 10* *Sex:* *I: 60% M* *C: 61% M* *Mean eGFR:* *I: 50 ± 13* *C: 51 ± 14* Groups comparable at baseline? Yes			<u>Incomplete outcome data</u>: As above	versus 6 of 281 patients in the saline group (P = 0.03) None of the CI-AKI patients developed a need for dialysis.	
Controlled diuresis for coronary angiography and/or percutaneous intervention							
Barbanti, 2016	Type of study: randomized controlled trial Setting: university hospital	Inclusion criteria: 1) All patients with symptomatic severe aortic stenosis undergoing TAVI were considered eligible Exclusion criteria:	Describe intervention (treatment/procedure/test): RenalGuard therapy received hydration with a normal saline solution; with an initial bolus (priming) of 250 ml was infused over 30 min (preprocedural. Urine	Describe control (treatment/procedure/test): control group received sodium normal saline solution at a rate of 1 ml/kg/h 12 h before TAVR, during contrast exposure, and for 6 h after the	<u>Length of follow-up</u>: 78 hrs <u>Loss-to-follow-up</u>: No loss to follow-up	Outcome measures and effect size (include 95%CI and p-value if available): AKI (defined: absolute	Authors' conclusion *'In summary, furosemide-induced diuresis with matched isotonic*

	Country: Italy Source of funding: not reported	1) chronic end-stage renal failure on dialysis; 2) episode of acute congestive heart failure with left ventricular ejection fraction <30% in the past 30 days before randomization; 3) contraindica-tions to placement of a Foley catheter; 4) urgent TAVI 5) unavailability of the RenalGuard system. <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 82 (78-83)* *C: 81 (78-84)* *Sex:* *I: 61% F* *C: 59% F* *Serum creatine ± SD* *I: 1.0 (0.85-1.15)* *C: 0.97 (0.83-1.16)* Groups comparable at baseline? Yes	flow was monitored and maintained at the target value throughout the procedure and during the following 4 h. phase).	procedure.		reduction in kidney function (<72 h) and defined as: 1) stage 1: increase in serum creatinine to 150% to 200% (1.5 to 2.0x increase compared with baseline) or increase of >0.3 mg/dl (≥26.4 mmol/l); 2) stage 2: increase in serum creatinine to 200% to 300% (2.0 to 3.0x increase compared with baseline); and 3) stage 3: increase in serum creatinine to ≥300% (>3_ increase compared with baseline) or serum creatinine of ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l).) I: 4 (5.4%) C: 13 (25.2%) RR: 0.21, 95% CI: 0.06 – 0.71 P=0.014 Cardiovascular	*intravenous hydration using the RenalGuard system is an effective therapeutic tool to reduce the occurrence of AKI in patients undergoing TAVR.'*

						death I: 0/56(0%) C: 1/56 (1.8%) P=0.306 Death I: 1/56 (1.8%) C: 2/56 (3.6%) P=0.537	
Brar, 2014	Type of study: randomized controlled trial Setting: elective patients, 1 center Country: United states of America Source of funding: not reported	Inclusion criteria: 1) patients referred to the cardiac catheterisation laboratory 2) an estimated glomerular fi ltration rate (GFR) of 60 mL/min per 1 ・73 m^2 or lower; 3) age 18 years or older; 4) at least one of the following: diabetes mellitus, history of congestive heart failure, hypertension (blood pressure >140/90 mm Hg or treatment with antihypertensive medication), or age older than 75 years. Exclusion criteria: 1) inability to	Describe intervention (treatment/procedure/test): 0.9% sodium chloride bolus infusion at 3 mL/kg for 1 h The fl uid rate was adjusted according to the left ventricular end-diastolic pressure as follows: 5 mL/kg/h for left ventricular end-diastolic pressure lower than 13 mmHg, 3 mL/kg/h for pressure of 13–18 mmHg, and 1.5 mL/kg/h for pressure higher than 18 mmHg. The fl uid rate was set at the start of the procedure (before contrast exposure), continued for the duration of the procedure, and for 4 h post-procedure.	Describe control (treatment/procedure/test): 0.9% sodium chloride bolus infusion at 3 mL/kg for 1 h 5 mL/kg per h. The fl uid rate was set at the start of the procedure (before contrast exposure), continued for the duration of the procedure, and for 4 h post-procedure.	Length of follow-up: 2-8 weeks for laboratory parameters 6 months for clinical events Loss-to-follow-up: Intervention: 0 (0%) Control: 0 (0%) Incomplete outcome data: Intervention: 18/196 (9%) 12 had 1 sCr value 6 had no sCr value Control:	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=a greater than 25% or 0.5 mg/dL increase in the serum creatinine concentration) I: 12/178 (7%) C: 28/172 (16%) RR: 0.41, 95% CI: 0.22 – 0.79, p=0.005 6-months mortality I: 0.5% C: 4% P=0.037 No significant difference in other adverse clinical events at 30 days or 6 months	Authors' conclusion: Left ventricular end-diastolic pressure-guided fl uid administration seems to be safe and eff ective in preventing contrast-induced acute kidney injury in patients undergoing cardiac catheterisation.

		obtain consent from participants, 2) emergency cardiac catheterisation (eg, primary percutaneous coronary intervention for ST-segment elevation myocardial infarction), 3) renal replacement therapy, 4) exposure to radiographic contrast media within the previous 2 days, 5) allergy to radiographic contrast media, 6) acute decompensated heart failure, 7) severe valvular heart disease, 8) mechanical aortic prosthesis, 9) left ventricular thrombus, 10) history of kidney or heart transplantation, 11) change in estimated GFR of			28/200 (14%) 24 had 1 sCr value 4 had no sCr value	In total, six patients (1・5%)—three in each group—terminated the intravenous fl uids early, the reason for which was shortness of breath in all six patients.	

		7.5% or more per day or a cumulative change of 15% or more during the pre ceding 2 or more days. <u>N total at baseline</u>: Intervention: 196 Control: 200 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 71 ± 9* *C: 72 ± 8* *Sex:* *I: 64% M* *C: 59% M* *eGFR ± SD* *I: 48 ± 9* *C: 48 ± 9* Groups comparable at baseline?					
Briguori, 2011	Type of study: randomized controlled trial Setting: elective patients, multicenter	<u>Inclusion criteria</u>: 1) patients with chronic kidney disease scheduled for coronary and/or peripheral angiography and/or angioplasty with an estimated	Describe intervention (treatment/procedure/test): hydration with normal saline plus NAC controlled by the RenalGuard system NAC was administered only iv (1500 mg in 1L saline) during the 3	Describe control (treatment/procedure/test): 154 mEq/L sodium bicarbonate in dextrose and H2O. The initial intravenous bolus was 3 mL/kg per hour for at least 1 hour before contrast injection. Then, all patients received the same fluid at	<u>Length of follow-up</u>: 1 week <u>Loss-to-follow-up</u>: 0 (0%) in both groups	Outcome measures and effect size (include 95%CI and p-value if available): CI-AKI (=an increase in sCr concentration ≥0.3	Authors' conclusion: RenalGuard therapy is superior to sodium bicarbonate and N-acetylcysteine

	Country: Italy Source of funding: not reported	glomerular filtration rate (eGFR) ≤30mL /min/ 1.73 m^2 and/or a risk score ≥11) <u>Exclusion criteria</u>: 1) acute myocardial infarction; 2) acute pulmonary edema; 3) cardiogenic shock; 4) dialysis; 5) multiple myeloma; 6) administration of sodium bicarbonate, theophilline, dopamine, mannitol, and/or fenoldopam; 7) recent (<48 hours) administration of iodinated contrast medium 8) enrollement in another study <u>N total at baseline</u>: Intervention: 146 Control: 146	phases (preprocedural, intraprocedural, and postprocedural) of the RenalGuard therapy.	a rate of 1 mL/kg per hour during contrast exposure and for 6 hours after the procedure. NAC orally at a dose of 1200 mg twice daily the day before and the day of administration of the contrast agent (for a total of 2 days) additional NAC dose (1200 mg diluted in 100 mL normal saline) was administered intravenously during the procedure. The total NAC dose was 6 g.	<u>Incomplete outcome data</u>: Intervention: 0 (0%) Control: 3/147 (2%) 2 discontinued treatment 1 did not receive allocated treatment	mg/dL above the baseline value at 48 hours after administration of Contrast or the need fordialysis) I: 16/146 (11%) C: 30/146 (21%) Odds ratio: 0.47, 95% CI 0.24 – 0.92 P<0.05	in preventing contrast-induced acute kidney injury in high-risk patients. The risk score for predicting CI-AKI was calculated according to the following algorithm: hypotension (integer score 5), intra-aortic balloon pump support (integer score 5), congestive heart failure (integer score 4), age >75 years (integer score 4), diabetes mellitus (integer score 3), eGFR _60 mL/min/1.73 m^2 (integer score 2 to 6), preexisting anemia(integer score 3), and CM volume (integer score 1 for each 100 cm^3). The global scores ≥5, 6 to 10, 11 to 16, and _16

		Important prognostic factors[2]: *For example* *age ± SD:* *I: 76 ± 8* *C: 75 ± 9* *Sex:* *I: 61% M* *C: 71% M* *eGFR ± SD:* *I: 32 ± 7* *C: 32 ± 9* Groups comparable at baseline? Yes					predict a CI-AKI risk of 7.5%, 14%, 26.1%, and 57.3%, respectively.
Marenzi, 2012	Type of study: randomised controlled trial Setting: elective and emergency patients Country: Italy Source of funding: not reported	Inclusion criteria: 1) age ≥18 years and ≤85 years, and elective or urgent (within 24 h from hospital admission because of non–ST-segment elevation [acute] myocardial infarction [NSTEMI]) coronary angiography and, when indicated, percutaneous coronary intervention (PCI). Exclusion criteria: 1) primary or rescue PCI and	Describe intervention (treatment/procedure/test): Approximately 90 min before the coronary procedure, Furosemide with matched hydration treatment was started with an initial intravenous bolus (250 ml) of normal saline solution over 30 min. Furosemide was then administered as a single intravenous bolus of 0.5 mg/kg (up to a maximum of 50 mg). Urine output was calculated continuously by the system, and when a urine output rate >300 ml/h was achieved, patients were brought to the catheterization laboratory and underwent	Describe control (treatment/procedure/test): continuous intravenous infusion of isotonic saline at a rate of 1 ml/kg/h (0.5ml/kg/h in case of left ventricular ejection fraction ≤40%) for at least 12 h before and 12 h after the procedure.	Length of follow-up: 72 hours Loss-to-follow-up: Intervention: 2/89 (2%) Failed to insert foley catheter Control: 2/85 (2%) Withdrawal of treatment due to pulmonary edema	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=a ≥25% or ≥0.5 mg/dl rise in serum creatinine over baseline during the first 72 h post-procedure) I: 4 (5%) C: 15 (18%) P=0.005 Cumulative in-hospital complications	Authors' conclusion: In patients with CKD undergoing coronary procedures, furosemide-induced high urine output with matched hydration significantly reduces the risk of CIN and may be associated with improved in-hospital outcome.

		angiography procedures requiring a direct renal injection of contrast, 2) cardiogenic shock, overt congestive heart failure, 3) acute respiratory insufficiency, 4) recent acute kidney injury, 5) chronic peritoneal or hemodialysis treatment, 6) known furosemide hypersensitivity, 7) receipt of intravenous contrast within 10 days before the procedure or another planned contrast-enhanced procedure in the following 72 h, 8) contraindications to placement of a Foley catheter in the bladder. <u>N total at baseline</u>: Intervention: 87 Control: 83	coronary angiography. Matched hydration was continued throughout the catheterization procedure and for 4 h after the last contrast dose. At this time, therapy was discontinued. Additional doses of furosemide (up to a maximal cumulative dose of 2.0 mg/kg) were given in cases where the urine output was below 300 ml/h during treatment. The Foley catheter was removed 24 h after the procedure.		<u>Incomplete outcome data</u>: As described above)	I: 8% C: 18% P=0.052	

		Important prognostic factors[2]: *For example* *age ± SD:* *I: 73 ± 7* *C: 74 ± 8* *Sex:* *I: 78% M* *C: 78% M* *eGFR ± SD:* *I: 1.8 ± 0.6* *C: 1.7 ± 0.5* Groups comparable at baseline? Yes					
Qian, 2016	Type of study: randomised controlled trial Setting: elective patients, multiple centers Country: Japan Source of funding: not reported	Inclusion criteria: 1) patients with CKD and chronic heart failure undergoing coronary procedures Exclusion criteria: - N total at baseline: Intervention: 132 Control: 132 Groups comparable at baseline? Yes	Describe intervention (treatment/procedure/test): Central-venous pressure guided hydration group	Describe control (treatment/procedure/test): Standard hydration group	Length of follow-up: 48 hours Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=an increase by >25% or >0.5 mg/dl of the serum creatinine level within 2 days after the procedure) I: 16% C: 30% P=0.006 Acute heart failure: I: 3.8%	Authors' conclusion: Controlled vnous pressure guided fluid administration can safely and effectively reduce the risk of CIN in patients with CKD and chronic heart failure.

						C: 3.0% P=0.50	
Usmiani, 2015	Type of study: randomized controlled trial Setting: elective patients Country: Brazil Source of funding: not reported	Inclusion criteria: 1) patients with chronic kidney disease (CKD) undergoing coronary procedures Exclusion criteria: - N total at baseline: Intervention: 65 Control: 68 Groups comparable at baseline? Yes	Describe intervention (treatment/procedure/test): iv 250 mL isotonic saline bolus, followed by a 0.5 mg/kg furosemide i.v. bolus to forced diuresis. A dedicated device automatically matched the isotonic saline i.v. infusion rate to the urinary output for 1 h before, during and 4 h after the procedure.	Describe control (treatment/procedure/test): Standard saline and bicarbonate hydration	Length of follow-up: 2 days Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CI-AKI (=an increase by >25% or >0.5 mg/dl of the serum creatinine level within 2 days after the procedure) I: 7% C: 25% P=0.01 Major adverse cardiovascular events I: 7% C: 32% P<0.01	Authors' conclusion: In patients with CKD undergoing coronary procedures, furosemide-induced high urine output with matched hydration significantly reduces the risk of CIN and may be associated with improved in-hospital outcome.
Usmiani, 2016	Type of study: randomized controlled trial Setting: university hospital Country: Italy Source of funding: not	Inclusion criteria: 1) Elgibile for voth procedures 2) eGFR of less than 60 mL/min/1.73m2 Exclusion criteria: 1) primary PCI (emergency procedure); 2) cardiogenic shock;	Describe intervention (treatment/procedure/test): Matched hydration was to be performed with the Renal-Guard System. 250 mL i.v. isotonic saline bolus is given in 30 min, followed by 0.5 mg/kg i.v. furosemide to forced diuresis. Isotonic saline i.v. infusion proceeds automatically,	Describe control (treatment/procedure/test): BS-NAC intravenous hydration (isotonic saline/ N-acetylcysteine/vitamin C) 1000 mL isotonic saline i.v. administration 12 h before procedure (rate-adjusted according to LVEF 20–40mL/h if LVEF<30%, 80–120 mL/h if LVEF	Length of follow-up: 7 days Loss-to-follow-up: 9 loss to follow-up I: 8/67 C: 1/66	Outcome measures and effect size (include 95%CI and p-value if available): AKI (CIAKI after coronary angiography/PCI as defined by an increase of sCr +0.3	Authors' conclusion *'Matched hydration was more effective than BS-NAC in CIAKI prevention.'*

	reported	3) acute heart failure; 4) endstage renal disease on haemodialysis; 5) urinary tract infections within the last 3 months; 6) benign prostatic hyperplasia and; 7) previously known difficulties in urinary catheterization. <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I1: 76 ± 9* *C: 75 ± 8* *Sex:* *I1: 22% F* *C: 29% F* *Serum creatine ± SD* *I1: 1.54 ±0.43* *C: 1.42 ±0.41* Groups comparable at baseline? Yes	rate-matched with diuresis	30–50%, 200 mL/h if LVEF >50%). Plus 3 mL/kg/h 1.4% SB solution i.v. infusion for 1 h before Plus: 5000mg p.o. Vitamin C Plus: 1200mg p.o. N-acetylcysteine		mg/dL in 48 h or +50% in 7 days) I: 4 (6%) C: 16 (24%) P=0.01 Cardiovascular death I: 1/59(1.7%) C: 7/65 (10.8%)	

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures**
2. **Provide data per treatment group on the most important prognostic factors [(potential) confounders]**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders**

CAG: Cardiac angiography; CI-AKI: contrast-induced acute kidney injury; CIN: contrast induced nephropathy; CKD: chronic kidney disease; CT: computed tomography; CTPA: computed tomography – pulmonary angiography; ia: intra-arterial; IQR: intra quartile range; iv: intra-venous; NAC: N-acetylcysteine; PCI: percutaneous coronary intervention; sCr: serum creatinine

Search description

Systematic reviews

Database	Search terms	Total
Medline (OVID) 2000-heden Engels, Nederlands	1 exp Contrast Media/ or ((contrast adj3 iodine) or (contrast adj3 medi*)).ti,ab. (108416) 2 Sodium Chloride/ or exp Cardiac Catheterization/ or exp Bicarbonates/ or Rehydration Solutions/ or exp Fluid Therapy/ or (hydrat* or prehydrat* or posthydrat* or rehydrat* or 'volume expansion' or (pre adj1 hydrat*) or (post adj1 hydrat*) or ((oral or iv or intravenous) adj1 (hydrat* or fluid)) or (sodium adj2 (chloride* or bicarbonate*)) or nacl or ((heart or cardiac) adj2 catheterization*)).ti,ab. (262412) 3 exp Kidney Diseases/ or (((kidney or renal) adj2 (disease* or injur* or failure*)) or nephropath* or (renal adj2 (insufficienc* or function* or disease* or failure*))).ti,ab. (525125) 4 1 and 2 and 3 (911) 5 (((contrast* or ci) adj2 (nephropath* or 'kidney injury' or aki or nephrotoxicity)) or cin or ciaki).ti,ab. (8859) 6 Sodium Chloride/ or exp Cardiac Catheterization/ or exp Bicarbonates/ or Rehydration Solutions/ or exp Fluid Therapy/ or (hydrat* or prehydrat* or posthydrat* or rehydrat* or 'volume expansion' or (pre adj1 hydrat*) or (post adj1 hydrat*) or ((oral or iv or intravenous) adj1 (hydrat* or fluid)) or (sodium adj2 (chloride* or bicarbonate*)) or nacl or ((heart or cardiac) adj2 catheterization*)).ti,ab. (262412) 7 5 and 6 (644) 8 4 or 7 (1049) 9 limit 8 to (yr="2000 -Current" and (dutch or english)) (775) 10 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (236842) 11 9 and 10 (69) – 66 uniek 12 (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/) (1459903) 13 9 and 12 (333) 14 13 not 11 (278)	177
Embase (Elsevier)	'contrast medium'/exp OR (contrast NEAR/3 iodine):ab,ti OR (contrast NEAR/3 medi*):ab,ti AND (hydrat*:ab,ti OR prehydrat*:ab,ti OR posthydrat*:ab,ti OR rehydrat*:ab,ti OR 'volume expansion':ab,ti OR (pre NEAR/1 hydrat*):ab,ti OR (post NEAR/1 hydrat*):ab,ti OR ((oral OR iv OR intravenous) NEAR/1 (hydrat* OR fluid)):ab,ti OR (sodium NEAR/2 (chloride* OR bicarbonate)):ab,ti OR nacl:ab,ti OR ((heart OR cardiac) NEAR/2 catheterization):ab,ti OR 'sodium chloride'/exp OR 'heart catheterization'/exp OR 'bicarbonate'/exp OR 'oral rehydration solution'/exp OR 'hydration'/exp) AND ('kidney disease'/exp OR 'kidney function'/exp OR ((kidney or renal) NEAR/2 (disease* OR injur* OR failure*)):ab,ti OR nephropath*:ab,ti OR (renal NEAR/2 (insufficienc* OR function* OR disease* OR failure*)):ab,ti) OR ('contrast induced nephropathy'/exp/dm_pc OR ((contrast* OR ci) NEAR/2 (nephropath* OR 'kidney injury' OR aki OR nephrotoxicity)):ab,ti OR cin:ab,ti OR ciaki:ab,ti AND (hydrat*:ab,ti OR prehydrat*:ab,ti OR posthydrat*:ab,ti OR rehydrat*:ab,ti OR 'volume expansion':ab,ti OR (pre NEAR/1 hydrat*):ab,ti OR (post NEAR/1 hydrat*):ab,ti OR ((oral OR iv OR intravenous) NEAR/1 (hydrat* OR fluid)):ab,ti OR (sodium NEAR/2 (chloride* OR bicarbonate)):ab,ti OR nacl:ab,ti OR ((heart OR cardiac) NEAR/2 catheterization):ab,ti OR 'sodium chloride'/exp OR 'heart catheterization'/exp OR 'bicarbonate'/exp OR 'oral rehydration solution'/exp OR 'hydration'/exp)) AND ([dutch]/lim OR [english]/lim) AND [embase]/lim AND [2000-2015]/py AND ('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) NOT 'conference abstract':it (484)	

	AND 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT (animal* NOT human*)), (137) - 82 uniek	
Cochrane (Wiley)	((contrast* OR ci) NEAR/2 (nephropath* OR 'kidney injury' OR aki OR nephrotoxicity)):ab,ti OR cin:ab,ti OR ciaki:ab,ti AND (hydrat*:ab,ti OR prehydrat*:ab,ti OR posthydrat*:ab,ti OR rehydrat*:ab,ti OR 'volume expansion':ab,ti OR (pre NEAR/1 hydrat*):ab,ti OR (post NEAR/1 hydrat*):ab,ti OR ((oral OR iv OR intravenous) NEAR/1 (hydrat* OR fluid)):ab,ti OR (sodium NEAR/2 (chloride* OR bicarbonate)):ab,ti OR nacl:ab,ti OR ((heart OR cardiac) NEAR/2 catheterization)) 15 CDR, 45 DARE 11 CR's niet relevant (CIN-HPV) >4 uniek, DARE 25 uniek, 2 niet relevant	

RCTs

Database	Search terms	Total
Medline (OVID) Engels, Nederlands 2000-juni 2015	1 exp Contrast Media/ or ((contrast adj3 iodine) or (contrast adj3 medi*)).ti,ab. (110323) 2 Sodium Chloride/ or exp Cardiac Catheterization/ or exp Bicarbonates/ or Rehydration Solutions/ or exp Fluid Therapy/ or (hydrat* or prehydrat* or posthydrat* or rehydrat* or 'volume expansion' or (pre adj1 hydrat*) or (post adj1 hydrat*) or ((oral or iv or intravenous) adj1 (hydrat* or fluid)) or (sodium adj2 (chloride* or bicarbonate*)) or nacl or ((heart or cardiac) adj2 catheterization*)).ti,ab. (263883) 3 exp Kidney Diseases/ or (((kidney or renal) adj2 (disease* or injur* or failure*)) or nephropath* or (renal adj2 (insufficienc* or function* or disease* or failure*))).ti,ab. (527891) 4 1 and 2 and 3 (918) 5 (((contrast* or ci) adj2 (nephropath* or 'kidney injury' or aki or nephrotoxicity)) or cin or ciaki).ti,ab. (8912) 6 Sodium Chloride/ or exp Cardiac Catheterization/ or exp Bicarbonates/ or Rehydration Solutions/ or exp Fluid Therapy/ or (hydrat* or prehydrat* or posthydrat* or rehydrat* or 'volume expansion' or (pre adj1 hydrat*) or (post adj1 hydrat*) or ((oral or iv or intravenous) adj1 (hydrat* or fluid*)) or (sodium adj2 (chloride* or bicarbonate*)) or nacl or ((heart or cardiac) adj2 catheterization*)).ti,ab. or Water/ or water.ti,ab. or D5w.ti,ab. or Isotonic Solutions/ or Hypotonic Solutions/ or (ringer* adj3 (lactate or solution*)).ti,ab. or ((hypotonic or isotonic) adj3 solution*).ti,ab. or Hydroxyethyl Starch Derivatives/ or (Hydroxyethy* adj3 starch*).ti,ab. (818303) 7 5 and 6 (733) 8 4 or 7 (1140) 9 limit 8 to (yr="2000 -Current" and (dutch or english)) (818) 10 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (240088) 11 9 and 10 (72) 12 (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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1471469) 13 9 and 12 (341) 14 13 not 11 (283) – 265 uniek 17 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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 Cross sectional.tw. or Cross-sectional studies/ or historically	572 RCTS 6 SRs new (177 SRs in earlier search strategy)

	controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (2160769) 22 21 not 19 (134) – vanaf 2007: 105 – 103 uniek –in afzonderlijk document	
Embase (Elsevier)	'contrast medium'/exp OR (contrast NEAR/3 iodine):ab,ti OR (contrast NEAR/3 medi*):ab,ti AND (hydrat*:ab,ti OR prehydrat*:ab,ti OR posthydrat*:ab,ti OR rehydrat*:ab,ti OR 'volume expansion':ab,ti OR (pre NEAR/1 hydrat*):ab,ti OR (post NEAR/1 hydrat*):ab,ti OR ((oral OR iv OR intravenous) NEAR/1 (hydrat* OR fluid*)):ab,ti OR (sodium NEAR/2 (chloride* OR bicarbonate)):ab,ti OR nacl:ab,ti OR ((heart OR cardiac) NEAR/2 catheterization):ab,ti OR water:ab,ti OR d5w:ab,ti OR (ringer* NEAR/3 (lactate OR solution*)):ab,ti OR ((hypotonic OR isotonic) NEAR/3 solution*):ab,ti OR (hydroxyethy* NEAR/3 starch*):ab,ti OR 'sodium chloride'/exp OR 'heart catheterization'/exp OR 'bicarbonate'/exp OR 'oral rehydration solution'/exp OR 'hydration'/exp OR 'water'/exp OR 'isotonic solution'/exp OR 'ringer lactate solution'/exp OR 'hetastarch derivative'/exp OR 'fluid balance'/exp) AND ('kidney disease'/exp OR 'kidney function'/exp OR (kidney NEAR/2 (disease* OR injur* OR failure*)):ab,ti OR nephropath*:ab,ti OR (renal NEAR/2 (insufficienc* OR function* OR disease* OR failure*)):ab,ti) OR ('contrast induced nephropathy'/exp/dm_pc OR ((contrast* OR ci) NEAR/2 (nephropath* OR 'kidney injury' OR aki OR nephrotoxicity)):ab,ti OR cin:ab,ti OR ciaki:ab,ti AND (hydrat*:ab,ti OR prehydrat*:ab,ti OR posthydrat*:ab,ti OR rehydrat*:ab,ti OR 'volume expansion':ab,ti OR (pre NEAR/1 hydrat*):ab,ti OR (post NEAR/1 hydrat*):ab,ti OR ((oral OR iv OR intravenous) NEAR/1 (hydrat* OR fluid*)):ab,ti OR (sodium NEAR/2 (chloride* OR bicarbonate)):ab,ti OR nacl:ab,ti OR ((heart OR cardiac) NEAR/2 catheterization):ab,ti OR water:ab,ti OR d5w:ab,ti OR (ringer* NEAR/3 (lactate OR solution*)):ab,ti OR ((hypotonic OR isotonic) NEAR/3 solution*):ab,ti OR (hydroxyethy* NEAR/3 starch*):ab,ti OR 'sodium chloride'/exp OR 'heart catheterization'/exp OR 'bicarbonate'/exp OR 'oral rehydration solution'/exp OR 'hydration'/exp OR 'water'/exp OR 'isotonic solution'/exp OR 'ringer lactate solution'/exp OR 'hetastarch derivative'/exp OR 'fluid balance'/exp)) AND ([dutch]/lim OR [english]/lim) AND [embase]/lim AND [2000-2015]/py AND ('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) NOT 'conference abstract':it NOT 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT (animal* NOT human*)) (517) – 307 uniek	

Observational studies

Database	Search terms	Total
Medline (OVID) Engels, Nederlands 2007-juni 2015	1 exp Contrast Media/ or ((contrast adj3 iodine) or (contrast adj3 medi*)).ti,ab. (110323) 2 Sodium Chloride/ or exp Cardiac Catheterization/ or exp Bicarbonates/ or Rehydration Solutions/ or exp Fluid Therapy/ or (hydrat* or prehydrat* or posthydrat* or rehydrat* or 'volume expansion' or (pre adj1 hydrat*) or (post adj1 hydrat*) or ((oral or iv or intravenous) adj1 (hydrat* or fluid)) or (sodium adj2 (chloride* or bicarbonate*)) or nacl or ((heart or cardiac) adj2 catheterization*)).ti,ab. (263883) 3 exp Kidney Diseases/ or (((kidney or renal) adj2 (disease* or injur* or failure*))	103 obs.

	or nephropath* or (renal adj2 (insufficienc* or function* or disease* or failure*))).ti,ab. (527891) 4 1 and 2 and 3 (918) 5 (((contrast* or ci) adj2 (nephropath* or 'kidney injury' or aki or nephrotoxicity)) or cin or ciaki).ti,ab. (8912) 6 Sodium Chloride/ or exp Cardiac Catheterization/ or exp Bicarbonates/ or Rehydration Solutions/ or exp Fluid Therapy/ or (hydrat* or prehydrat* or posthydrat* or rehydrat* or 'volume expansion' or (pre adj1 hydrat*) or (post adj1 hydrat*) or ((oral or iv or intravenous) adj1 (hydrat* or fluid*)) or (sodium adj2 (chloride* or bicarbonate*)) or nacl or ((heart or cardiac) adj2 catheterization*)).ti,ab. or Water/ or water.ti,ab. or D5w.ti,ab. or Isotonic Solutions/ or Hypotonic Solutions/ or (ringer* adj3 (lactate or solution*)).ti,ab. or ((hypotonic or isotonic) adj3 solution*).ti,ab. or Hydroxyethyl Starch Derivatives/ or (Hydroxyethy* adj3 starch*).ti,ab. (818303) 7 5 and 6 (733) 8 4 or 7 (1140) 9 limit 8 to (yr="2000 -Current" and (dutch or english)) (818) 10 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (240088) 11 9 and 10 (72) 12 (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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1471469) 13 9 and 12 (341) 14 13 not 11 (283) – 265 uniek 17 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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 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] (2160769) 22 21 not 19 (134) – vanaf 2007: 105 – 103 uniek –in afzonderlijk document	

Appendices to chapter 7.1

Evidence tables

Table: Exclusion after revision of full text

Author and year	Reason for exclusion
Aggarwal, 2014	Article not found
Atallah, 2004	Published before the SR of Liu, 2015
Ball, 2014	Review, not systematic
Barbieri, 2014	Did not include subgroup analyses with patients with renal dysfunction
Bidram, 2015	Patients with eGFR<60 excluded
Bouzas-Mosquera, 2009	Published before the search date of SR of Liu, 2015
Cheungpasitporn, 2015	Did not include subgroup analyses with patients with renal dysfunction
Gandhi, 2014	Overlapping with the systematic review of Liu, 2015, that was already included in the literature analysis
Giacoppo, 2014	Overlapping with the systematic review of Liu, 2015, that was already included in the literature analysis
Han, 2014	Included in the review of Liu, 2015
Hoshi, 2014	Renal function not compromised, observational study
Jo, 2015	Article not available
Jo, 2008	Included in the review of Liu, 2015
Kandula, 2010	Published before the SR of Liu, 2015
Kaya, 2013	Published before the SR of Liu, 2015
Kenaan, 2014	Renal function not compromised, observation study
Lee, 2014	Overlapping with the systematic review of Liu, 2015, that was already included in the literature analysis
Leoncini, 2014	Outcomes were the cardioprotective effects
Leoncini, 2014	Included in the review of Liu, 2015
Li, 2012	Published before the SR of Liu, 2015
Liu, 2014	Patients with eGFR of 30-90 mL/min/1.73m^2 included, compared rosuvastatin with atorvastatin
Mao, 2014	Did not include subgroup analyses with patients with renal dysfunction
Marenzi, 2015	Did not include subgroup analyses with patients with renal dysfunction
Munoz, 2011	Published before the SR of Liu, 2015
Ozhan, 2010	Published before the SR of Liu, 2015
Pappy, 2011	More recent SR available
Patti, 2014	Letter to the editor, substantial subgroup of patients has no renal dysfunction
Patti, 2008	Published before the SR of Liu, 2015
Patti, 2011	Included in the review of Liu, 2015
Peruzzi, 2014	No separate analysis for patients with renal dysfunction
Qiao, 2015	Patients with eGFR of 30-89 mL/min/1.73m^2 included
Quintavalle, 2012	Included in the review of Liu, 2015
Sanadgol, 2012	Published before the SR of Liu, 2015
Sanei, 2014	Patients with normal renal function included
Shehata, 2015	Patients with eGFR of 30-90 mL/min/1.73m^2 included
Singh, 2014	Overlapping with the systematic review of Liu, 2015, that was already included in the literature analysis
Takagi, 2011	More recent SR available
Toso, 2014	Used the data of Leoncini, 2013
Toso, 2010	Included in the review of Liu, 2015
Ukaigwe, 2014	Overlapping with the systematic review of Liu, 2015, that was already included in the literature analysis
Wu, 2015	Article not found
Xie, 2014	Overlapping with the systematic review of Liu, 2015, that was already included in the literature analysis
Xinwei, 2009	Published before the SR of Liu, 2015
Yoshida, 2009	Published before the SR of Liu, 2015
Yun, 2014	Observational study

Zhang, 2011	More recent SR available
Zhao, 2008	Published before the SR of Liu, 2015
Zhou, 2011	More recent SR available

Table: Exclusion after revision of full text (update 2017)

Author and year	Reason for exclusion
Ali-Hassan-Sayegh, 2016	Does not meet selection criteria, references were checked
Chalikias, 2016	Does not meet selection criteria, references were checked
Fan, 2016	No studies included after original search
Gadapa, 2016	Full text not available
Giacoppo, 2015	Full text not available
Jo, 2015	Does not meet selection criteria
Li, 2016	Does not meet selection criteria
Navarese, 2017	Does not meet selection criteria
Rabbat, 2015	Abstract
Subramaniam, 2016	Does not meet selection criteria, references were checked
Thompson, 2016	No studies included after original search
Vanmassenhove, 2016	No studies included after original search
Wang, 2016	No studies included after original search
Zografos, 2016	Full text not available
Zografos, 2016	No studies included after original search
Zografos, 2016	No studies included after original search
Fu, 2015	Full text not available
Gaskina, 2016	Abstract
Gaskina, 2016	Abstract
Maskon, 2016	Abstract
Park, 2016	Full text not available
Kohsravi, 2016	Does not meet selection criteria
Li, 2016	Does not meet selection criteria

Table of quality assessment for systematic reviews of RCTs and observational studies
Based on AMSTAR checklist (Shea et al.; 2007, BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher et al 2009, PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Liu, 2015	yes	Yes	No (excluded studies not referenced)	yes	NA	Yes	Unclear (different definitions of PC-AKI used among included studies)	Unclear (funnel plot not provided for subanalysis, <10 studies included)	Yes (none of the studies were sponsored by industry)

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs)**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table etc.)**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (e.g. Chi-square, I2)?**
8. **An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Risk of bias table for intervention studies (randomized controlled trials)
Research question:

Study reference (first author, publication year)	**Describe method of randomisation**[1]	**Bias due to inadequate concealment of allocation?**[2] (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?**[4] (unlikely/likely/unclear)	**Bias due to loss to follow-up?**[5] (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?**[6] (unlikely/likely/unclear)
Shehata, 2015	Not described	unclear	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Qiao, 2015	Not described	unclear	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Abaci, 2015	Not described	unclear	Unlikely	Unlikely	Unlikely	unlikely	Unclear	unclear

1. **Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.**
2. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..**
3. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
5. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear**
6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

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

Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Liu, 2015	SR and meta-analysis of RCTs	Inclusion criteria SR: RCTs investigating the	Describe intervention:	Describe control:	End-point of follow-up (PC-AKI):	Outcome measure-1: PC-AKI, defined as an	Facultative:

[individual study characteristics deduced from [1st author, year of publication]] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	*Literature search up to Feb 2014* **A**: Jo, 2008 **B**: Toso, 2010 **C**: Patti, 2011 **D**: Quintavalle, 2012 **E**: Han, 2013 **F**: Leoncini, 2013 <u>Study design</u>: RCT [parallel] <u>Setting and Country</u>: Not reported <u>Source of funding:</u> None was sponsored by industry	efficacy of statins in preventing CIN compared with placebo, the treatment groups received statins before the contrast exposure at any dose, for any length of time. Studies were only included if none of the arms or both received N-acetylcysteine. Exclusion criteria SR: Trials comparing 2 different doses of statins. Only studies that included patients with renal dysfunction (defined as eGFR≤60 mL/min/1.73m^2 or creatine clearance ≤60 mL/min/1.73m^2) were included here. *6 studies included* <u>Important patient characteristics at baseline</u>: <u>N</u> **A**: 236 **B**: 304 **C**: 74 **D**: 410 **E**: 450 **F**: 210 Groups comparable at baseline? Unclear	**A**: Simvastin 40mg, 12 hours for 2 days, 80mg before procedure, 80mg after the procedure **B**: Atorvastatin 80mg/d for 48 hours before and after the procedure versus placebo, oral NAC 1200mg 2 times day before to the day after procedure **C**: Atorvastatin 80 mg 12 hours before and further 40mg 2 hours before angiography **D**: 80mg within 24h before exposure, oral NAC 1200mg^2 times/day before and the day of procedure **E**: Rosuvastatin 10mg from 2 days before to 3 days after procedure **F**: Rosuvastin 40mg followed by 20mg/d, oral NAC 1200 mg 2 times/d before and day after procedure	**A**: Placebo **B**: Oral NAC 1200mg 2 times day before to the day after procedure **C**: Placebo **D**: Placebo, oral NAC 1200mg^2 times/day before and the day of procedure **E**: placebo **F**: oral NAC 1200 mg 2 times/d before and day after procedure	**A:** within 48h after contrast administration **B**: within 5 days **C**: 48h after PCI **D**: 48h after from baseline value **E**: within 72h after contrast administration **F**: within 72h after contrast administration <u>For how many participants were no complete outcome data available?</u> Not reported	increase of ≥25%SCr or SCr ≥0.5mg/dL within 48-120h. Effect measure: RR (95% CI: **A**: 0.75 (0.17;3.28) **B**: 0.94 (0.48;1.83) **C**: 0.56 (0.21;1.47) **D**: 0.44 (0.17;1.13) **E**: 0.82 (0.33;2.04) **F**: 0.41 (0.20;0.85) Pooled effect (fixed effects model): 0.51 (0.37;0.70) favouring intervention. I^2=44% <u>Outcome measure-2: Mortality (cases)</u> **A**: intervention=0, placebo=0 **B**: intervention=1, placebo=0 **C**: NR **D**: NR **E**: NR **F**: NR <u>Outcome measure-3: Start dialysis</u> **A**: intervention=0, placebo=1 **B**: intervention=0, placebo=1 **C**: NR **D**: NR **E**: NR **F**: NR <u>Outcome measure-4: ICU</u> (not reported in any of	The result presented here involves a subgroup analyses of patients with impaired kidney function. The results of the study of Quintavalle, 2012 are adapted (secondary outcome measure is the correct PC-AKI definition) Liu, 2015 include a fixed analyses, the use of random analyses might be preferred given the heterogeneity found (I^2=44%) For the outcome measures *mortality*, *start of dialysis* and *ICU admission*, data extraction took place using the original articles of the studies included in Liu, 2015.

						the included studies)	

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series])1
This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy – otherwise the evidence table for studies of diagnostic test accuracy should be used.

Research question:

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Shehata, 2015	Type of study: RCT Setting: Catheterization laboratory Country: Egypt Source of funding: not reported, no conflicts of interest	Inclusion criteria: Diabetic patients, carrying the diagnosis of chronic stable angina and suffering from mild or moderate CKD. (eGFR 30– <90 mL/min/1.73 m^2 Exclusion criteria: Severe CKD (e GFR <30 mL/min/1.73 m) [9], end-stage renal disease (or patients on hemodialysis), intake of potentially nephrotoxic drugs, acute myocardial infarction requiring emergency coronary intervention, cardiogenic shock. See article for a complete overview of exclusion criteria. N total at baseline: Intervention: 65 Control: 65 Important prognostic factors[2]:	Describe intervention (treatment/procedure/test): Oral atorvastatin (80 mg daily) for 48 h before PCI, in addition to periprocedural intravenous infusion of isotonic saline and oral N-acetylcysteine. Standard parenteral hydration protocol in both groups.	Describe control (treatment/procedure/test): Intravenous infusion of isotonic saline and oral N-acetylcysteine, in addition to placebo formula.	follow-up: 10 days Loss-to-follow-up: Intervention: 0 Control: 0 Incomplete outcome data: No	Outcome measures and effect size (include 95%CI and p-value if available): Incidence of PC-AKI (increase in serum creatinine of ≥0.5 mg/dL or an absolute increase of ≥25% from baseline <48 or72h after contrast exposure) Intervention group: 5/65 events, control group 13/65 events, p<0.05 Mortality, initiation of dialysis and ICU-admission not reported	The current study results identify a high-risk population showing a pronounced benefit upon adopting the high dose atorvastatin pretreatment approach before contrast exposure.

		For example *age ± SD:* *I: 55 (6)* *C:57 (5)* *Sex:* *I: 53% M* *C: 56% M* Contrast (mL) (mean*± SD)* *I: 274 (8)* *C: 278 (11)* Contrast nephropathy risk score (mean*± SD)* *I: NR* *C: NR* Groups comparable at baseline? yes, no statistical significant differences					
Qiao, 2015	Type of study: RCT Setting: Hospital Country: China Source of funding: not reported, no conflicts of interest	<u>Inclusion criteria</u>: 1. Diabetic patients; 2. Mild to moderate CKD, which was defined as estimated glomerular filtration rate (eGFR) 30 to 89 ml/min per 1.73 m2; 3. Total CM administrated dose of volume ≥ 100 ml. <u>Exclusion criteria</u>: Pregnancy, lactation, Ketoacidosis, Lactic acidosis, prior CM administration within 7 days of study entry. Importantly, all patients who were recent statin users (with 14 days before	Describe intervention (treatment/procedure /test): The rosuvastatin group received 10 mg everyday for at least 48 hours before and 72 hours after CM administration.	Describe control (treatment/proced ure/test): Received no statins during the trial. All patients received intravenous hydration with isotonic saline (0.9% sodium chloride 1-1.5 ml/kg/hour for 3-12 hours before and 6-24 hours after the procedure).	<u>follow-up</u>: Between 48-72h after procedure, up to 30 days. <u>Loss-to-follow-up</u>: Intervention: 0 Control: 0 <u>Incomplete outcome data</u>: No	Outcome measures and effect size (include 95%CI and p-value if available): Incidence of PC-AKI (increase in serum creatinine of ≥0.5 mg/dL or an absolute increase of ≥25% from baseline <48 or72h after contrast exposure) Intervention group: 2/60 events, control group 2/60 events, p<0.05 Mortality, initiation of dialysis and ICU-admission not specifically	

		the procedure) were excluded. See article for a complete overview of exclusion criteria. <u>N total at baseline</u>: Intervention: 60 Control: 60 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 62 (8)* *C:62 (8)* *Sex:* *I: 68% M* *C: 73% M* Contrast (mL) (mean*± SD)* *I: 204 (75)* *C: 212 (85)* Contrast nephropathy risk score (mean*± SD)* *I: NR* *C: NR* Groups comparable at baseline? Yes, average eGFR 60 ml/min/1.73 m^2				reported, but no post procedural adverse events occurred.	
Abaci, 2015	Type of study: RCT Setting: University cardiology institute, inpatients	<u>Inclusion criteria</u>: Patients naïve to statins and scheduled for coronary angiography with EGFR between 30 and 60 mL/min/1.73m^2. <u>Exclusion criteria</u>:	Describe intervention (treatment/procedure /test): Patients were given 40mg rosuvastatin <24 h before coronary angiography and	Describe control (treatment/proced ure/test): No statin treatment	<u>follow-up</u>: Between 48-72h after angiography, 6 months and 1 year. <u>Loss-to-follow-up</u>: Intervention: 7 (6%) Reasons unknown	Outcome measures and effect size (include 95%CI and p-value if available): Incidence of PC-AKI (increase in serum creatinine of ≥0.5 mg/dL or an absolute increase of	All patients received intravenous hydration with isotonic saline (14mL/kg/h, 0.9% sodium chloride) for 12h before and 24h after contrast exposure.

	Country: Turkey Source of funding: not reported, no conflicts of interest	Emergency coronary angiography, acute renal failure or end-stage renal failure requiring dialysis. See article for a complete overview of exclusion criteria. <u>N total at baseline</u>: Intervention: 110 Control:110 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 67.5 (8.9)* *C:67.7 (8.9)* *Sex:* *I: 64% M* *C: 73.4% M* Contrast (mL) (mean*± SD)* *I: 139.2 (77.4)* *C: 117.7 (56.8)* Contrast nephropathy risk score (mean*± SD)* *I: 9.3 (3.9)* *C: 7.7 (3.4)* Groups comparable at baseline? Not completely, see contrast volume and contrast nephropathy risk (above)	hereafter 20mg/day for 2 days.		Control: 5 (5%) Reasons unknown <u>Incomplete outcome data</u>: See loss to follow-up	≥25% from baseline <48 or72h after contrast exposure. Intervention group: 6/103 events, control group 9/105 events. Relative risk (95%CI)= 0.71 (0.25;-2.0) Mortality, initiation of dialysis and ICU-admission not reported	Statistical analyses not clear. Secondary outcomes (death and decrease in eGFR of ≥25% or renal failure requiring dialysis at 12 months) were reported as a composite outcome and exact data was not shown.

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures**

2. **Provide data per treatment group on the most important prognostic factors [(potential) confounders]**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders**

Search description

Database	Search terms	Total
Medline (OVID) 1995-aug. 2015 Engels, Nederlands	1 exp Contrast Media/ or ((contrast adj3 iodine) or (contrast adj3 medi*)).ti,ab. (112282) 2 exp Kidney Diseases/ or (((kidney or renal) adj2 (disease* or injur* or failure*)) or nephropath* or (renal adj2 (insufficienc* or function* or disease* or failure*))).ti,ab. (536907) 3 1 and 2 (8955) 4 (((contrast* or ci) adj2 (nephropath* or 'kidney injury' or aki or nephrotoxicity)) or ciaki).ti,ab. (1969) 5 3 or 4 (9449) 6 limit 5 to (yr="1995-Current" and (dutch or english)) (5521) 7 exp hydroxymethylglutaryl-coa reductase inhibitors/ or (statin* or lovastatin* or meglutol* or pravastatin* or simvastatin* or rosuvastatin* or atorvastatin*).).ti,ab,kw. or (hydroxymethylglutaryl* adj4 inhibitor*).ti,ab,kw. (45277) 8 6 and 7 (131) 9 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (248141) 10 8 and 9 (32) – 31 uniek 11 (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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1508278) 12 8 and 11 (71) 13 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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 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] (2209511) 14 8 and 13 (38) 15 12 not 10 (45) 22 (12 or 14) not 10 (58) – 56 uniek	131
Embase (Elsevier)	'contrast induced nephropathy'/exp/dm_pc OR ((contrast* OR ci) NEAR/2 (nephropath* OR 'kidney injury' OR aki OR nephrotoxicity)):ab,ti OR ciaki:ab,ti OR ('contrast medium'/exp OR (contrast NEAR/3 iodine):ab,ti OR (contrast NEAR/3 medi*):ab,ti AND ('kidney disease'/exp OR 'kidney function'/exp OR (kidney NEAR/2 (disease* OR injur* OR failure*)):ab,ti OR nephropath*:ab,ti OR (renal NEAR/2 (insufficienc* OR function* OR disease* OR failure*)):ab,ti)) AND ('hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp/mj OR statin*:ab,ti OR lovastatin*:ab,ti OR meglutol*:ab,ti OR pravastatin*:ab,ti OR simvastatin*:ab,ti OR rosuvastatin*:ab,ti OR atorvastatin*:ab,ti OR (hydroxymethylglutaryl* NEAR/4 inhibitor*):ab,ti) AND ([dutch]/lim OR [english]/lim) AND [embase]/lim AND [1995-2015]/py 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp)) (34) – 6 uniek AND ('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) NOT 'conference abstract':it OR 'clinical study'/exp (87) – 38 uniek	

Appendices to chapter 7.2

Evidence tables

Table: Exclusion after revision of full text

Author and year	Reason for exclusion
ACT Investigators, 2009	description of study design, not an original article
Amini, 2009	Prehydration only, not comparable to Dutch clinical practice
Ashworth, 2010	overlaps with Loomba, 2013 and is a less recent review
Azmus, 2005	Not specifically patients with normal or abnormal kidney function (mix of impaired kidney function and diabetics)
Bagshaw, 2006	review, not systematic
Berwanger, 2012	Sub-analysis of ACTT studty (which is already included in literature analysis)
Briguori, 2011	Does not compare N-acetylcysteine to placebo
Briguori, 2007	Not specifically patients with normal or abnormal kidney function (mix of impaired kidney function and diabetics)
Brown, 2009	overlaps with Loomba, 2013 and is a less recent review
Burns, 2010	Not specifically patients with normal or abnormal kieny function (mix of impaired kidney function and diabetics)
Busch, 2013	overlaps with Loomba, 2013 and is a less recent review
Buyukhatipoglu, 2010	outcome measures as described in PICO not reported
Calabro, 2011	observational study
Carbonell, 2010	already included in Loomba 2013, and Sun, 2013
Carbonell, 2007	already included in Loomba 2013, and Sun, 2013
Chen, 2008	does not compare no NAC to NAC (both treatment arms recieve NAC)
Coyle, 2006	Not specifically patients with normal or abnormal kidney function (mix of impaired kidney function and diabetics)
Duong, 2005	overlaps with Loomba, 2013 and is a less recent review
Gomes, 2005	Not specifically patients with normal or abnormal kidney function (mix of impaired kidney function and diabetics)
Gonzales, 2007	overlaps with Loomba, 2013 and is a less recent review
Gouveira, 2015	review, not systematic
Gulel, 2005	already included in Loomba 2013
Gurm, 2011	Does not answer study question
Hafiz, 2012	Acetylcysteine not compared to control
Hassan, 2011	observational study
Housseinjani, 2013	review, not systematic
Hsu, 2012	already included in review Wu 2013
Hsu, 2007	already included in review Wu 2013
Izcovich, 2015	systematic review, poor quality (no clear description of included studies)
Jo, 2009	does not compare no NAC to NAC
Juergens, 2010	does not compare no NAC to NAC (both treatment arms recieve NAC)
Khalili, 2006	Prehydration only, not comparable to Dutch clinical practice
Kim, 2010	already included in Loomba 2013
Kotlyar, 2005	Dubbel met Kotlyar, 2005
Lee, 2011	does not compare no NAC to NAC (both treatment arms recieve NAC)
Liu, 2006	overlaps with Loomba, 2013 and is a less recent review
Marenzi, 2006	Not specifically patients with normal or abnormal kidney function (mix of impaired kidney function and diabetics)
Mittal, 2014	review, not systematic
Momeni, 2012	Observational study
O'Sullivan 2013	Does not answer reseach question broadly enough, used for cross refernecing
Ratcliffe, 2009	Not specifically patients with normal or abnormal kidney function (mix of impaired kidney function and diabetics)
Ritz, 2006	letter to the editor, not an original article
Sandhu, 2006	Unclear if patients were hydrated next to the NAC administration or not
Sar, 2010	Not specifically patients with normal or abnormal kidney function (mix of impaired

	kidney function and diabetics)
Shabbir, 2015	Article not found
Shalansky, 2006	review, not systematic
Solomon, 2014	review, not systematic
Staniloae, 2009	subanalysis of trial, observational data
Thiele, 2010	already included in Loomba 2013
Trivedi, 2009	overlaps with Loomba, 2013 and is a less recent review
Zagler, 2006	overlaps with Loomba, 2013 and is a less recent review

Risk of bias table for intervention studies (randomized controlled trials)
Research question:

Study reference (first author, publication year)	**Describe method of randomisation**[1]	**Bias due to inadequate concealment of allocation?**[2] (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?**[4] (unlikely/likely/unclear)	**Bias due to loss to follow-up?**[5] (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?**[6] (unlikely/likely/unclear)
CT scan, normal kidney function								
Hsu, 2012	Computer-generated random numbers	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
CT scan, decreased kidney function								
Kama, 2014	By website randomization.com	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Kitzler, 2012	Not reported	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear	Unclear
Poletti, 2007	Randomized by serial enrolment	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Poletti, 2013	Computer generated randomization list	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unlikely
Tepel, 2000	"Randomly assigned"	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unlikely
CAG or PCI, normal kidney function								
Carbonell, 2007	Computer-generated random numbers	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Jaffery,	"Randomly	Unlikely	Unlikely	Unlikely	Unlikely	Likely	Unlikely	Unclear

2012	assigned"							
Kim, 2010	Computer-generated random numbers	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Kinbara, 2010	"Randomly assigned"	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Lawlor, 2004	"randomization was performed by the hospital clinical trials pharmacist"	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Sadat, 2011	Computer generated randomization scheme	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Tanaka, 2011	"Randomly assigned"	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Thiele, 2010	Computer generated random numbers	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
CAG or PCI, decreased kidney function								
ACT, 2011	24-hour Web-based automated randomization system	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely
Castini, 2010	Computer generated randomization table	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Ferrario, 2009	Computer generated randomization list	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Gulel,	Random	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear

2005	allocation table							
Habib, 2016	Patients were randomized into three groups	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Izani Wan (Mohamed), 2008	Computer generated randomization list	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear
Koc, 2012	Not described	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Kotlyar, 2005	Not described	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Sadineni, 2017	Patients were randomly assigned	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Seyon, 2007	Not described	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear

1. **Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.**
2. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..**
3. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
5. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear**
6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series])1
This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy – otherwise the evidence table for studies of diagnostic test accuracy should be used.

Research question:

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
CT scan, normal kidney function							
Hsu, 2012	Type of study: Randomized controlled trial Setting: emergency department, medical teaching center Country: Taiwan Source of funding: non-commercial	Inclusion criteria: 1) all adult patients who received chest or abdominal contrast-enchanced computed tomography (CECT) Exclusion criteria: 1) patients undergoing long-term hemodialysis or peritoneal hemodialysis 2) patients who received another dose of contrast medium within 72 hours 3) patient refused to sign concent forms 4) patients had a knon allergic reaction to N-acetlycysteine (NAC) N total at baseline: Intervention: 106 Control: 103 Important prognostic factors[2]: *For example age ± SD:*	Describe intervention (treatment/procedure/test): 600mg NAC In 0.9% sodium chloride (3 mL/kg/h) for 60 minutes prior to the CECT 0.9% sodium chloride (1 mL/kg/h) for 6 hours after CECT	Describe control (treatment/procedure/test): 0.9% sodium chloride (3 mL/kg/h) for 60 minutes prior to the CECT 0.9% sodium chloride (1 mL/kg/h) for 6 hours after CECT	Length of follow-up: 72 hours Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN05: (=a rise in SCr ≥0.5mg/dL within 48-72 hours after CECT imaging) I: 7.5% C: 14.6% Odds Ratio (OR): 0.31 (95% CI: 0.10 – 0.96, p=0.04) CINor: (=a rise in SCr ≥0.5mg/dL or 25% within 48-72 hours after CECT imaging) I: 11.3% C: 19.4% OR: 0.35 (95% CI: 0.13 – 0.91, 0=0.03) Mortality: I: 7.5% C: 12.6% OR: 0.49 (95% CI: 0.15 – 1.55, p=0.22)	Authors' conclusion: A singe dose of NAC before CECT imagingcan prevent CIN in an ED setting. However it does not improve mortality rate or the need for dialysis. Patients with congestive pulmonary edema received an adjusted hydration schedule where the rates of fluid loading were decreased by 50%.

		I: 80 ± 9 *C: 80 ± 11* *Sex:* *I: 74% M* *C: 76% M* *Baseline SCr (mg/dL) ± SD* *I: 1.40 ± 0.58* *C: 1.26 ± 0.43* Groups comparable at baseline?				Permanent renal replacement therapy: 0% in both groups	
CT scan, decreased kidney function							
Kama, 2014	Type of study: randomized controlled trial Setting: emergency department, academic tertiary hospital Country: Turkey Source of funding: not reported	<u>Inclusion criteria</u>: 1) adult patients (≥18 years) who presented to the emergency department 2) patients who received CECT as part of their emergency care 3) moderate or high risk for contrast induced nephropathy (CIN) according to Mehran score (>5) <u>Exclusion criteria</u>: 1) CIN risk determine as Low by Mehran score 2) history of contrast-related allergies 3) hemodynamically unstable patients requiring resuscitation or surgery 4) patients receiving renal replacement therapy 5) patients did not provide	Describe intervention (treatment/procedure/test): 150mg/kg NAC In 1000mL in 0.9% saline at the rate of 350ml/hour for 3 hours Before, after and during administration of contrast	Describe control (treatment/procedure/test): 1000mL 0.9% saline at the rate of 350ml/hour for 3 hours Before, after and during administration of contrast	<u>Length of follow-up</u>: 48-72 hours Patients who were diagnosed with CIN – 1 months <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=25% increase or greater than 0.5mg/dL (44µmol/L) increase in the serum creatinine level, 48-72 hours after administration of the contrast agent compared with the baseline creatinine measurement) I: 7 (19%) C: 5 (14%) p>0.05 No contrast- or treatment-induced adverse events were detected during emergency department care	Authors'conclusion: None of the short-term protocols with normal saline or NAC was superior in the emergency department pateints requiring CECT who had a moderate or high risk of CIN.

		infomed consent <u>N total at baseline</u>: Intervention: 36 Control: 35 <u>Important prognostic factors</u>[2]: *For example* *age (95% CI):* *I: 69 (65-73)* *C: 67 (62-72)* *Sex:* *I:69 % M* *C: 65% M* *eGFR <20 mL/min/1.73m^2* *I: 25%* *C: 9%* *eGFR 40-20 mL/min/1.73m^2* *I: 36%* *C: 46%* *eGFR 60-40mL/min/1.73m^2* *I: 11%* *C: 14%* Groups comparable at baseline? Yes					
Kitzler, 2012	Type of study: randomized controlled trial Setting: single-center,	<u>Inclusion criteria</u>: -patients with chronic kidney disease stage 1-4 undergoing elective computer-assisted tomography with non-ionic radiocontrast agents when	Describe intervention (treatment/procedure/test): N-acetylcysteine 4800mg per os	Describe control (treatment/procedure/test): 0.45% saline, 1mL/kg/h over 24 hours	<u>Length of follow-up</u>: Not reported <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome</u>	Outcome measures and effect size (include 95%CI and p-value if available): No patients developed contrast induced acute kidney injury.	Authors' conclusion: Following radiocontrast administration neither vitamin E nor NAC in addition to saline demonstrated an additional beneficial

	elective patients Country: Source of funding:	compared to 0.45% saline alone <u>Exclusion criteria</u>: - <u>N total at baseline</u>: Intervention: 10 Control: 10 <u>Important prognostic factors</u>[2]: *For example* *age ± SD: mean: 75 years* *(not reported per group)* *Sex:* *38% M* *(not reported per group)* Groups comparable at baseline? Unc;ear	0.45% saline, 1mL/kg/h over 24 hours		<u>data</u>: Not reported	There was no significant difference in serum creatinine change between the three study arms.	effect on kidney fi=unction when compared to saline alone.
Poletti, 2007	Type of study: randomized controlled trial Setting: emergency patients Country: Switzerland Source of funding: not reported	<u>Inclusion criteria</u>: 1) patients admitted consecutively to the emergency department during daytime hours 2) serum creatinine >1.2md/dL <u>Exclusion criteria</u>: 1) pregnancy 2) end stage renal failure with dialysis 3) suspicion of acute renal obstruction 4) asthma	Describe intervention (treatment/procedure/test): 900mg NAC diluted in 5% glucose solution administered iv 1 hour before CT 0.45% saline iv at a rate of 5mL/kg body weight over the course of an hour	Describe control (treatment/procedure/test): placebo in 5% glucose solution administered iv 1 hour before CT 0.45% saline iv at a rate of 5mL/kg body weight over the course of an hour before CT	<u>Length of follow-up</u>: 4 days <u>Loss-to-follow-up</u>: 7 (8%) 3 died, 3 left hospital 1 transferred to another hospital (not reported per group) <u>Incomplete outcome data</u>: As above	Outcome measures and effect size (include 95%CI and p-value if available): Nephrotoxicity (=≥25% increase in serum creatinine value) I: 2/44 (5%) C: 9/43 (21%) P=0.026	Authors' conclusion: On the basis of the serum creatinine concentration, iv administration of NAC appears protective against the nephrotoxicity of contrast medium.

		5) severe cardiac failure 6) hemodynamically unstable condition contraindicating iv hydration 7) nonurgent indications for CT <u>N total at baseline</u>: 87 Intervention: 44 Control: 43 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 70 ± 19* *C: 73 ± 17* *Sex:* *I: 59% M* *C: 67% M* Groups comparable at baseline? Yes	before CT 900mg NAC mixed into the 0.45% saline perfusion administered iv after completion of CT at a rate of 1mL/kg body weight per hour for 12 hours	placebo mixed into the 0.45% saline perfusion administered iv after completion of CT at a rate of 1mL/kg body weight per hour for 12 hours			
Poletti, 2013	Type of study: randomized controlled trial Setting: emergency department patients Country: Switzerland	<u>Inclusion criteria</u>: 1) patients admitted consecutively to the emergency department 2) estimated creatinine clearance by MDRD of <60ml/min/1.73m^2 <u>Exclusion criteria</u>: 1) asthma 2) pregnancy 3) obstructive nephropathy	Describe intervention (treatment/procedure/test): 6000mg NAC iv diluted in 100mL saline, administered in the 60 minutes before the CT-scan Hydration of 250mL	Describe control (treatment/procedure/test): placebo diluted in 100mL saline, administered in the 60 minutes before the CT-scan Hydration of 250mL of 0.45%	<u>Length of follow-up</u>: 10 days <u>Loss-to-follow-up</u>: Intervention: 3 (5%) Reasons not reported Control: 1 (2%) Reasons not reported	Outcome measures and effect size (include 95%CI and p-value if available): Nephropathy (=increase of at least 25% or 44µmol/l in serum creatinine level at day 2,4 or 10 compared to day 0) I: 8 (15%) C: 10 (17%) P=0.99	Authors' conclusion: An ultra-high dose of intravenous NAC is ineffective at preventing nephrotoxicity in patients with renal impairment undergoing emergency contrast CT.

	Source of funding: not reported	4) patient's refusal N total at baseline: 104 Intervention: 55 Control: 59 Important prognostic factors[2]: *For example* *age ± SD:* *I: 78 ± 12* *C: 78 ± 12* *Sex:* *I: 49% M* *C: 51% M* Groups comparable at baseline? Yes	of 0.45% saline before CT-scan 1000mL saline 0.45% after CT-scan	saline before CT-scan 1000mL saline 0.45% after CT-scan	Incomplete outcome data: As above	Composite event of death or acute kidney injury I: 33% C: 24% p-value not reported	
Tepel, 2000	Type of study: Randomized controlled trial Setting: elective patients receiving CT-scan at hospital Country: Germany Source of funding: not reported	Inclusion criteria: 1) patients with a serum creatinine >1.2mg/dL or creatinine clearance <50mL/min 2) known chronic renal failure and a stable serum creatinine concentration 3) patients receiving elective CT-scans Exclusion criteria: 1) acute renal failure N total at baseline: Intervention: 41 Control: 42	Describe intervention (treatment/procedure/test): Acetylcycsteine orally 600mg twice daily on the day before and on the day of administration of the contrast agent Saline (0.45%) iv. 1ml/kg/h for 12 hours before and 12 hours after contrast administration	Describe control (treatment/procedure/test): Saline (0.45%) iv. 1ml/kg/h for 12 hours before and 12 hours after contrast administration	Length of follow-up: 48 hours, 6 days Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Increase of at least 0.5mg/dL (44µmol/L) in serum creatinine concentration 48 hours after administration of contrast agent: I: 1/41 (2%) C: 9/42 (21%) RR: 0.1 (95% CI: 0.01 – 0.9) P=0.01 None of the patients required dialysis	Authors' conclusion: Prophylactic administration of the antioxidant acetylcysteine, along with hydration, prevents the reduction in renal function induced by iopromide, a non-ionic, low-osmolality contrast agent, in patients with chronic renal insufficiency.

		Important prognostic factors[2]: *For example* *age ± SD:* *I: 66±11* *C: 65 ± 15* *Sex:* *I:59 % M* *C: 55% M* Groups comparable at baseline? Yes					
CAG or PCI, normal kidney function							
Carbonell, 2007	Type of study: randomized controlled trial Setting: tertiary hospital, cardiac unit Country: Spain Source of funding: not reported	Inclusion criteria: 1) patients with acute coronary syndrome and normal renal function, admitted to the cardiac unit and referred for cardiac catheterization 2) angina at rest or post-myocardial infarction Or they had received thrombolytic therapy with failed recanalization so the cardiac catheterisation was an emergency procedure Exclusion criteria: 1) chronic renal failure or acute renal dysfunction 2) hemodynamic instability (systolic blood pressure <90mmHg) 3) known allergy to NAC or contrast agents	Describe intervention (treatment/procedure/test): NAC (600mg diluted in 50mL of 0.9% saline) iv for 30 minutes twice daily for a total of 4 times Starting at least for 6 hours before the administration of contrast media 0.9% saline iv at least 6 hours before procedure, maintained for 12 hours after contrast dosing	Describe control (treatment/procedure/test): placebo (diluted in 50mL of 0.9% saline) iv for 30 minutes twice daily for a total of 4 times Starting at least for 6 hours before the administration of contrast media 0.9% saline iv at least 6 hours before procedure, maintained for 12 hours after contrast dosing	Length of follow-up: 48 hours Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Contrast induced nephropathy (=an acute increase in the serum creatinine concentration ≥0.5mg/dL and/or >25% increase above baseline level at 48 hours after contrast dosing) I; 10.3% C: 10.1% P=0.50 None of the patients required dialysis.	Patients with congestive heart failure received a reduced hydration volume. Authors' conclusion: The prophylactic administration of intravenous NAC provides no additional benefit to saline in high-risk coronary patients with normal renal function.

		4) untreated gastrointestinal bleeding 5) previous treatment with theophylline, mannitol or nephrotoxic antibiotics <u>N total at baseline</u>: Intervention: 107 Control: 109 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 63 ± 14* *C: 61 ± 12* *Sex:* *I: 80% M* *C: 73% M* *Creatinine clearance (ml/min)* *I: 86 ± 29* *C: 88 ± 30* Groups comparable at baseline?					
Jaffery, 2012	Type of study: randomized controlled trial Setting: single-center inpatients, emergency	<u>Inclusion criteria</u>: 1) patients hospitalized with a primary diagnosis of acute coronary syndrome 2) scheduled for coronary angiography (CAG) or intervention during this hospitalization 3) age ≥18 years	Describe intervention (treatment/procedure/test): NAC: 1200mg bolus followed by 200mg/h for 24	Describe control (treatment/procedure/test): Placebo in 500ml 5% dextrose solution of water iv	<u>Length of follow-up</u>: 72 hours for lab parameters 30 days for mortality and hospital stay <u>Loss-to-follow-up</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=increase in serum creatinine concentration ≥25% above the baseline level within 72 hours of	Patients with clinical evidence of heart failure received only NAC iv or placebo Authors' conclusion: In acute coronary syndrome patients undergoing CAG with or

	procedure Country: United States of America Source of funding: not reported	<u>Exclusion criteria</u>: 1) end stage renal disease requiring dialysis 2) hypersensitivity to NAC 3) history of life-threatening contrast reaction <u>N total at baseline</u>: Intervention: 192 Control: 206 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 66 ± 13* *C: 65 ± 13* *Sex:* *I: 67 % M* *C: 59 % M* *Baseline creatinine clearance (ml/min)* *I: 87 ± 41* *C: 92 ± 44* Groups comparable at baseline? Yes	hours In 500ml 5% dextrose solution of water iv Normal saline (0.9%) iv; 1/ml/kg for 24 hours	Normal saline (0.9%) iv; 1/ml/kg for 24 hours	<u>Incomplete outcome data</u>: Not reported	the administration of intravenous contrast) I: 16% C: 13% P=0.40 Outcomes of mortality and length of hospital not reported.	without percutaneous intervention (PCI), high-dose intravenous NAC failed to reduce the incidence of CIN.
Kim, 2010	Type of study: randomized controlled trial Setting:	<u>Inclusion criteria</u>: 1) patients scheduled for elective CAG and/or PCI with apparently normal renal function	Describe intervention (treatment/procedure/test): Oral acetylcysteine	Describe control (treatment/procedure/test): 0.9% saline 1/mL/kg/h for 12	<u>Length of follow-up</u>: 48 hours <u>Loss-to-follow-up</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=increase in sCR of at	Authors' conclusion: Not relevant – based on cystatin-C defined CIN results and not the sCR based CIN.

	elective patients, one hospital Country: South Korea Source of funding: not reported	<u>Exclusion criteria</u>: 1) acute coronary syndrome requiring emergency CAG/PCI 2) cardiogenic shock 3) iodinated contrast media administration within a monthor NAC within 48 hours before study entry 4) current dialysis or a serum creatinine >1.4mg/dL for men or >1.2mg/dL for women 5) thyroid diseases 6) allergy to the study medication <u>N total at baseline</u>: Intervention: 80 Control: 86 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 62 ± 11* *C: 62 ± 10* *Sex:* *I: 79% M* *C: 67% M* *SCr (mg/dL)* *I: 1.03 ± 0.17* *C: 1.03 ± 0.14*	600mg twice a day on the day before and the day of coronary angiography 0.9% saline 1/mL/kg/h for 12 hours before and 6hours after CAG	hours before and 6hours after CAG	<u>Incomplete outcome data</u>: Not reported	least 0.5mg/dL or >25% within 48 hours of contrast exposure) I: 3.8% C: 8.1% p>0.05	

		Groups comparable at baseline? Yes					
Kinbara, 2010	Type of study: randomized controlled trial Setting: elective patients, one hospital Country: Japan Source of funding: not reported	<u>Inclusion criteria</u>: 1) Patients with stable coronary artery disease scheduled to undergo CAG and/or PCI, with stable serum creatinine concentrations <u>Exclusion criteria</u>: 1) acute myocardial infarction 2) use of vasopressors before PCI 3) cardiogenic shock 4) current peritoneal or hemodialysis 5) planned post-contrast dialysis 6) allergies to ths study medications 7) congestive heart disease 8) severe valvular disease 9) pregnancy 10) multiple myeloma 11) amyloidosis <u>N total at baseline</u>: Intervention: 15 Control: 15 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 70 ± 10*	Describe intervention (treatment/procedure/test): NAC 704mg orally twice daily on the day before ond on the day of CAG and/or PCI 0.9% saline iv 1/ml/kg/hour For 30 minutes before and 10 hours after angiography	Describe control (treatment/procedure/test): 0.9% saline iv 1/ml/kg/hour For 30 minutes before and 10 hours after angiography	<u>Length of follow-up</u>: 48 hours <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=SCr increase of >0.5mg/dL from baseline to 48 hours to angiography) I: 0 (0%) C: 4 (27%) 96% CI: 0.10 – 5.991, p=0.011	Authors' conclusion: These results suggest that both prophylactic NAC and aminophylline administration are effective in preventing CIN, but not with hydration alone.

		C: 70 ± 8 *Sex:* *I: 80% M* *C: 80% M* *SCr (mg/dL)* *I: 1.00 ± 0.36* *C: 0.94 ± 0.21* Groups comparable at baseline? Yes					
Lawlor, 2004	Type of study: randomized controlled trial Setting: elective patients, single center Country: United Kingdom Source of funding: not reported	Inclusion criteria: 1) patients with peripheral vascular disease going for elective angiography or angioplasty to participate in this trial Exclusion criteria: - N total at baseline: Intervention: 46 Control: 48 Important prognostic factors[2]: *For example* *age ± SD:* *I: 72 ± 12* *C: 69 ± 12* *Sex:* *I: 59% M* *C: 69% M*	Describe intervention (treatment/procedure/test): 1g of NAC in each bag of 0.9% saline 0.9% saline (500mL over 4-6 hours) 6-12 hours prior to angiography and again after angiography	Describe control (treatment/procedure/test): 0.9% saline (500mL over 4-6 hours) 6-12 hours prior to angiography and again after angiography with placebo	Length of follow-up: 7 days Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=a rise of 25% or 0.5mg/dL in sCR at 48 hours after contrast administration) Patients with normal kidney function: I: 0/29 (0%) C: 0/27 (0%) p>0.05 Patients with decreased kidney function: I: 3/17 (18%) C: 3/21 (14%) p>0.05	Authors' conclusion: NAC pre-contrast and post-contrast does not confer any benefit in preventing radiocontrast induced nephropathy in vascular patients

		SCr (µmol/L) *I: 110 ± 42* *C: 124 ± 63* Groups comparable at baseline? Yes					
Sadat, 2011	Type of study: randomized controlled trial Setting: elective patients, single center Country: United Kingdom Source of funding: no funding	Inclusion criteria: 1) patients undergoing peripheral angiography for peripheral artery disease Exclusion criteria: 1) patients with established renal failure – on renal replacement therapy N total at baseline: Intervention: 21 Control: 19 Important prognostic factors[2]: *For example* *age ± SD:* *I: 75 ± 11* *C: 70 ± 14* *Sex:* *Not reported* Groups comparable at baseline? Unclear	Describe intervention (treatment/procedure/test): NAC 600mg twice daily orally on the ay before and on the day of CAG (2.4g in total) Iv hydration 0.9% saline 1L over 12 hours before CAG 1L over 12 hours after CAG	Describe control (treatment/procedure/test): Iv hydration 0.9% saline 1L over 12 hours before CAG 1L over 12 hours after CAG	Length of follow-up: 72 hours Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=0.5mg/dL or 25% increase in sCr from baseline value within 48 hours of exposure to intravascular radiographic contrast media that is not attributable to other causes) I: 1/21 (5%) C: 3/19 (16%) P=0.33	Authors' conclusion: A clear conclusion is not formulated.
Tanaka, 2011	Type of study: randomized controlled trial	Inclusion criteria: 1) patients admitted for ST-segment elevation acute myocardial infarction	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	Length of follow-up: 36 hours Loss-to-follow-up:	Outcome measures and effect size (include 95%CI and p-value if available):	Authors' conclusion: While N=acetylcysteine might have the possibility

	Setting: emergency patients, single center Country: Japan Source of funding: not reported	treated with primary PCI <u>Exclusion criteria</u>: 1) dialysis 2) known allergy to NAC 3) inability to take NAC orally <u>N total at baseline</u>: Intervention: 38 Control: 38 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 63 ± 13* *C: 61 ± 14* *Sex:* *I: 82% M* *C: 82% M* *SCr (mg/dL)* *I: 0.95 ± 0.34* *C: 0.88 ± 0.25* Groups comparable at baseline? Yes	NAC 705mg orally before and 12, 24, 26 pours after intervention (2.8g in total) Hydration with iv Ringer lactate solution at a rate of 1-2ml/kg/hour for more than 12 hours after primary CAG	Hydration with iv Ringer lactate solution at a rate of 1-2ml/kg/hour for more than 12 hours after primary CAG	Not reported <u>Incomplete outcome data</u>: Not reported	CIN (=an increase in sCr level of 25% or more from baseline value within 72 hours after primary angioplasty) I: 2/38 (5%) C: 5/38 (13%) P=0.21 No major adverse events (death, acute renal failure requiring temporary replacement therapy, need for mechanical ventilation) occurred in either group during the in-hospital follow-up period.	to reduce the incidence of contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction, the in-hospital mortality and morbidity were not significantly different between the two groups.
Thiele, 2010	Type of study: randomized controlled trial Setting: emergency patients, one	<u>Inclusion criteria</u>: 1) patients with acute myocardial infarction undergoing primary PCI 2) symptoms <12 hours and ST-segment elevation ≥0.1mV in ≥2 extremity leads or ≥o.2 mV in ≥2 ore-	Describe intervention (treatment/procedure/test): NAC intravenous bolus	Describe control (treatment/procedure/test): 10mL of 0.9% saline at each injection	<u>Length of follow-up</u>: Laboratory parameters: 72 hours Clinical endpoints: 6 months <u>Loss-to-follow-up</u>: none	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=increase in sCr of ≥25% from baseline within 72 hours after PCI)	Authors' conclusion: High-dose iv NAC does not provide additional clinical benefit to placebo with respect to CIN in non-selected patients undergoing angioplasty

	tertiary hospital Country: Germany Source of funding: not reported	cordial leads <u>Exclusion criteria</u>: 1) previous fibrinolysis <12 hours 2) known NAC allergy 3) chronic dialysis 4) pregnancy 5) contra-indications for magnetic resonance imaging <u>N total at baseline</u>: Intervention: 126 Control: 125 <u>Important prognostic factors</u>[2]: *For example* *age (interquartile range):* *I: 68 (57-75)* *C: 68 (56-76)* *Sex:* *I: 71% M* *C: 66% M* *SCr (µmol/L; interquartile range)* *I: 81 (69-97)* *C: 78 (67-90)* Groups comparable at baseline? Yes	1200mg before CAG And 1200mg twice daily for 48 hours (total dose 6g) Hydration with intravenous 0.9% saline; infusion rate 1ml/kg/hour for 12 hours (or 0.5mg/kg/h in overt heart failure)	Hydration with intravenous 0.9% saline; infusion rate 1ml/kg/hour for 12 hours (or 0.5mg/kg/h in overt heart failure)	<u>Incomplete outcome data</u>: none	I: 18/126 (14%) C: 25/125 (20%) P=0.28 Mortality after 6 months I: 12/126 (14%) C: 12/125 (14%) p>0.05 New congestive heart failure I: 11/126 (9%) C: 7/125 (6%) p>0.05	with moderate doses of contrast medium and optimal hydration.
CAG or PCI, decreased kidney function							
ACT, 2011	Type of study: randomized	<u>Inclusion criteria</u>: 1) patients undergoing	Describe intervention	Describe control (treatment/proced	<u>Length of follow-up</u>: 48-96 hours for	Outcome measures and effect size (include 95%CI	Authors' conclusion

	controlled trial Setting: inpatients, elective, multi-centre Country: Brazil Source of funding: non-commercial	CAG or peripheral arterial angiography 2) at least one risk factor for CI-AKI: -age >70 years -chronic renal failure -diabetes mellitus -clinical evidence of congestive heart failure -left ventricular ejection fraction <0.45 -hypotension <u>Exclusion criteria</u>: -patients on dialysis -patients with ST-segment elevation myocardial infarction -pregnancy or breastfeeding -women <45 years who did not use contraceptive methods <u>N total at baseline</u>: Intervention: 1172 Control: 1136 With eGFR<30 ml/min I: 68 C: 63 With eGFR 30 to 60 ml/min I: 515 C: 492 <u>Important prognostic</u>	(treatment/procedure/test): NAC 2x600mg orally every 12 hours for 2 days (2 doses before and 2 doses after contrast administration, total dose 4800mg) Hydration with 0.9% saline 1mg/kg/hour from 6-12 hours before to 6-12 hours after angiography	ure/test): placebo orally every 12 hours for 2 days (2 doses before and 2 doses after contrast administration) Hydration with 0.9% saline 1mg/kg/hour from 6-12 hours before to 6-12 hours after angiography	laboratory parameters 30 days for clinical events <u>Loss-to-follow-up</u>: Intervention: 56 (5%) 12 did not receive study drug before angiography 15 were not submitted to angiography 19 were lost to 48-96 hour serum creatinine follow-up 4 died before 48-96 hours 15 did not return to collect serum creatinine 1 was lost to 30-day follow-up Control: 54 (5%) 7 did not receive study drug before angiography 12 were not submitted to angiography 17 were lost to 48-96 hour serum creatinine follow-up 3 died before 48-96 hours 14 did not return to collect serum creatinine 1 was lost to 30-day follow-up <u>Incomplete outcome data</u>:	and p-value if available): CI-AKI (=a 25% elevation of sCr above baseline 48-986 hours after angioplasty) All participants I: 147/1153 (12.7%) C: 142/119 (12.7%) RR: 1.00 (95% CI: 0.81 – 1.25, p=0.97) Patients with serum creatinine >1.5mg/dL: I: 12/188 (6%) C: 10/179 (6%) P=0.75 Patients with eGFR 30 – 60 mL/min I: 30/425 (7%) C: 27/398 (7%) RR: 1.04 (0.63 – 1.72) P=0.73 Patients with eGFR<30ml/min I: 6/56 (11%) C: 3/48 (6%) RR: 1.71 (0.45 – 6.49) P=0.92 Composite outcome of death or need for dialysis:	In this large randomized trial we found that acetylcysteine does not reduce the risk of contrast-induced acute kidney injury or other clinically relevant outcomes in at-risk patients undergoing coronary or peripheral vascular angiography.

		factors[2]: *For example* *age ± SD:* *I: 68 ± 10* *C: 68 ± 10* *Sex:* *I: 62% M* *C:61 % M* Groups comparable at baseline? Yes			Intervention: 1153 (98%) had data included in laboratory parameters analysis 1171 (99.9%) had data included in secondary outcome analysis Reasons not reported Control: 1119 (98%) had data included in laboratory parameters analysis 1135 (99.9%) had data included in secondary outcome analysis Reasons not reported	I: 2,2% C: 2.3% Hazard ratio (HR): 0.97 (95% CI: 0.56 – 1.69, p=0.92) Cardiovascular deaths: HR: 0.99 (95% CI: 0.51 – 1.99, p=0.97) There was also no difference in the risk of these outcomes defined post hoc.	
Castini, 2008	Type of study: randomized controlled trial Setting: elective patients, single centre Country: Italy Source of funding: not reported	Inclusion criteria: 1) patients undergoing CAG and/or PCI 2) age ≥18 years 3) stable sCr ≥1.2mg/dL Exclusion criteria: 1) sCr >4mg/dL 2) a history of dialysis, multiple myeloma, pulmonary edema, cardiogenic shock, acute myocardial infarction 3) emergency catheterization 4) recent exposure to radiographic contrast media within 7 days of the study 5) allergy to iodinate	Describe intervention (treatment/procedure/test): NAC 600mg orally every 12 hours for 2 days (2 doses before and 2 doses after contrast administration, total dose 2400mg) 0.9% saline iv 1ml/kg/hour for 12 hours before and 12 hours after contrast administration	Describe control (treatment/procedure/test): 0.9% saline iv 1ml/kg/hour for 12 hours before and 12 hours after contrast administration	Length of follow-up: 5 days Loss-to-follow-up: none Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN1 (=increase in sCr ≥25% over the baseline value in any of the time points: 24, 48 and 120 hours after contrast administration) I: 7 (14%) C: 9 (17%) p>0.05 CIN2 (=increase in sCr ≥0.5mg/dL over the	Authors' conclusion Our findings suggest that the addition of NAC does not add further benefit in CIN prevention, compared to standard hydration with isotonic saline infusion.

		contrast media or NAC 6) previous enrolment in the same or other protocols 7) administration of mannitol, theophylline, dopamine, dobutamine, nonsteroidal anti-inflammatory drugs or fenoldopam N total at baseline: Intervention: 52 Control: 51 Important prognostic factors[2]: *For example* *age ± SD:* *I: 71 ± 7* *C:73 ± 8* *Sex:* *I: 94% M* *C: 84% M* *sCr (mg/dL)* *I: 1.57 ± 0.38* *C: 1.49 ± 0.30* Groups comparable at baseline? Yes				baseline value in any of the time points: 24, 48 and 120 hours after contrast administration) I: 4 (8%) C: 5 (9%) p>0.05 No acute renal failure necessitating renal replacement therapy occurred.	
Ferrario, 2009	Type of study: randomized controlled trial	Inclusion criteria: 1) patients scheduled for elective or diagnostic CAG and/or PCI 2) age ≥18 years	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	Length of follow-up: 3 days Loss-to-follow-up: Intervention:	Outcome measures and effect size (include 95%CI and p-value if available): CIN	Authors' conclusion In our experience, NAC did not prevent CIN in patients receiving iso-

	Setting: elective patients, university hospital Country: Italy Source of funding: not reported	3) creatinine clearance <55ml/min and a stable renal function <u>Exclusion criteria</u>: 1) ongoing acute myocardial infarction or acute coronary syndrome 2) renal replacement therapy 3) allergy to NAC 4) need for administration of mannitol, theophylline, dopamine, dobutamine, fenoldopam or nephrotoxic drugs within 1 week of procedure 5) clinical signs of dehydration and systemic hypotension <u>N total at baseline</u>: Intervention: 99 Control: 101 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 75 ± 8* *C: 75 ± 7* *Sex:* *I: 68% M* *C: 62% M* *Creatinine clearance*	NAC 600mg orally every 12 hours for 2 days (2 doses on the day before and 2 doses on the day of contrast administration, total dose 2400mg) 0.9% saline 1ml/kg/h in 12-24 hours before the procedure and 24 hours after	Placebo (glucose tablets) orally every 12 hours for 2 days (2 doses on the day before and 2 doses on the day of contrast administration) 0.9% saline 1ml/kg/h in 12-24 hours before the procedure and 24 hours after	4 (4%) Reasons not reported Control: 4 (3%) Reasons not reported <u>Incomplete outcome data</u>: Not reported	(=increase in sCr ≥0.5mg/dL or >25% within 3 days after the procedure) I: 8/99 (8%) C: 6/101 (6%) P=0.60	osmolar (iodixanol) contrast media and adequate hydration.

		(mL/min) *I: 37 ± 11.5* *C: 40 ± 9.3* Groups comparable at baseline? Yes					
Gulel, 2005	Type of study: randomized controlled trial Setting: elective, single centre Country: Turkey Source of funding: not reported	<u>Inclusion criteria</u>: 1) patients scheduled for elective diagnostic CAG 2) chronic renal impairement: sCr >1.3mg/dL 3) stable renal function <u>Exclusion criteria</u>: 1) acute renal failure 2) end-stage renal failure on regular dialysis 3) clinically evident heart failure 4) allergy against contrast agents 5) serious hepatic dysfunction 6) planned PCI <u>N total at baseline</u>: Intervention: 25 Control: 25 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 61 ± 12* *C: 62 ± 12*	Describe intervention (treatment/procedure/test): NAC 600mg orally every 12 hours for 2 days (2 doses on the day before and 2 doses on the day of contrast administration, total dose 2400mg) 0.9% saline 1ml/kg/h in 12 hours before the procedure and 12 hours after	Describe control (treatment/procedure/test): 0.9% saline 1ml/kg/h in 12 hours before the procedure and 12 hours after	<u>Length of follow-up</u>: 48 hours <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Contrast nephropathy (= an increase more than 0.5 mg/dL 48 hours after the procedure compared with baseline values-) I: 3/25 (12%) C: 2/25 (8%) p>0.05	Authors' conclusion: Our results show that oral acetylcysteine does not reduce the risk of contrast nephropathy when used before elective diagnostic CAG in patients with renal dysfunction.

		Sex: *I: 80% M* *C: 72% M* *Creatinine clearance (mL/min)* *I: 46.5 ± 4.2* *C: 43.2 ± 3.9* Groups comparable at baseline? Yes					
Habib, 2016	Type of study: randomized controlled trial Setting: European Gaza Hospital, Gaza, Palestine (Israel) Source of funding: not reported	<u>Inclusion criteria</u>: Patients had at least one risk factor for CIN (age >70 years, baseline creatinine level >1.5 mg/dL, heart failure, diabetes mellitus or contrast media volume >300 mL) <u>Exclusion criteria</u>: Not stated <u>N total at baseline</u>: Group A: 40 Group C: 40 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *Group A: 63 ± 8* *Group C: 63 ± 8* *Sex:* *Group A: 67% M* *Group C: 76% M*	Describe intervention (treatment/procedure/test): Group A (n = 30), NAC 1200 mg orally before angiography and 1200 mg orally twice daily for three doses along with good hydration	Describe control (treatment/procedure/test): Group C (n = 45), hydration with 0.9% saline started just before contrast media injection and continued for 12 h at a rate 1.0 mL/kg/min after angiography or 0.5 mL/kg/h in cases with overt heart failure for 12 h	<u>Length of follow-up</u>: 48 hours <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Contrast nephropathy (= an increase more than 0.5 mg/dL 48 hours after the procedure compared with baseline values-) I: 2/30 C: 8/45 P=0.001	Authors' conclusion: Our study indicates that high doses of NAC plus hydration provide better protection against CIN than combination therapy of NAC and ascorbic acid plus hydration, or hydration alone.

		Groups comparable at baseline? Yes					
Izani Wan, 2008 (Mohamed)	Type of study: randomized controlled trial Setting: elective patients, single centre Country: Malaysia Source of funding: not reported	<u>Inclusion criteria</u>: 1) patients electively admitted for CAG 2) calculated creatinine clearance 40-90ml/min 3) age ≥18 years <u>Exclusion criteria</u>: 1) severe renal failure 2) presence of acute or reversible component of renal failure 3) severe peptic ulcer disease 4) history of allergy to NAC 5) severe asthma 6) pregnancy or breastfeeding <u>N total at baseline</u>: Intervention: 49 Control: 51 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 58 ± 8* *C: 56 ± 7* *Sex:* *I: 86% M* *C: 82% M*	Describe intervention (treatment/procedure/test): NAC 600mg orally every 12 hours for 2 days (2 doses on the day before and 2 doses on the day of contrast administration, total dose 2400mg) 0.45% saline 1ml/kg/h in 12 hours before the procedure and 12 hours after	Describe control (treatment/procedure/test): 0.45% saline 1ml/kg/h in 12 hours before the procedure and 12 hours after	<u>Length of follow-up</u>: 48 hours <u>Loss-to-follow-up</u>: Intervention: 4 (8%) 1 early discharge 2 procedure cancellation 1 procedure complication Control: 4 (7%) 2 early discharge 2 procedure cancellation <u>Incomplete outcome data</u>: As above	Outcome measures and effect size (include 95%CI and p-value if available): CIN (= increase of >25% in the sCr level 48 hours after the procedure) I: 2/49 (4%) C: 6/51 (12%) P=0.27 None of the patients who developed CIN required dialysis.	Authors' conclusion: Addition of NAC to standard hydration therapy is not associated with reduction in incidence of CIN in patients with mild to moderate renal impairment undergoing elective CAG.

		SCr (µmol/L) I: 124 *± 17* *C: 124 ± 22* Groups comparable at baseline? Yes					
Koc, 2012	Type of study: randomized controlled trial Setting: elective patients, single centre Country: Turkey Source of funding: not reported	<u>Inclusion criteria</u>: 1) patients about to undergo CAG and/or PCI 2) calculated creatinine clearance <60ml/min or sCr≥1.1mg/dL 3) age ≥18 years <u>Exclusion criteria</u>: 1) contrast-agent hypersensitivity 2) pregnancy or lactation 3) decompensated heart failure 4) pulmonary edema 5) emergency catheterisation 6) acute or end-stage renal failure <u>N total at baseline</u>: Intervention: 80 Control: 80 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 62 ± 10* *C: 65 ± 11*	Describe intervention (treatment/procedure/test): NAC 600mg intravenously every 12 hours for 2 days (2 doses on the day before and 2 doses on the day of contrast administration, total dose 2400mg) 0.9% saline iv 1ml/kg/h in on the day before, on the day of, and on the day after the procedure	Describe control (treatment/procedure/test): 0.9% saline iv 1ml/kg/h in on the day before, on the day of, and on the day after the procedure	<u>Length of follow-up</u>: 48 hours <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=baseline sCr ≥25% and/or an absolute increase in sCr of ≥0.5 mg/dL 48 hours after the procedure) I: 2 (3%) C: 13 (16%) P=0.006 No patients needed hemodialysis.	Authors'conclusion: The results of this study suggest that NAC plus high-dose hydration was superior to high-dose hydration alone as well as standard hydration for the protection of renal function in patients with mild to moderate renal dysfunction who are undergoing CAG and/or PCI.

		Sex: *I: 76% M* *C: 79% M* *Creatinine clearance (mL/min)* *I: 59 ± 16* *C: 58 ± 16* Groups comparable at baseline? Yes					
Kotlyar, 2005	Type of study: randomised controlled trial Setting: elective patients admitted for 1 day Country: Australia Source of funding: commercial (pharmaceutical company)	<u>Inclusion criteria</u>: 1) day-stay elective patients scheduled for CAG and/or PCI <u>Exclusion criteria</u>: 1) allergy to the study medication 2) unstable renal function 3) undergoing chronic dialysis 4) uncontrolled asthma 5) pregnancy or breastfeeding <u>N total at baseline</u>: I1: 20 I2: 21 C: 19 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I1: 66 ± 14* *I2: 67 ± 12*	Describe intervention (treatment/procedure/test): I1: NAC 300mg intravenously, once 1-2 hours before procedure and once 2-4 hours after procedure (total dose 600mg) Hydration iv: 0.9% saline 100ml/hour 2 hours before procedure and 5hours after procedure I1: NAC6300mg intravenously, once 1-2 hours before	Describe control (treatment/procedure/test): Hydration iv: 0.9% saline 100ml/hour 2 hours before procedure and 5hours after procedure	<u>Length of follow-up</u>: 2-4 days and 30 days <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): None of the patients developed CIN (= None of the patients developed a need for dialysis.	Authors' conclusion: For day-saty patients with mild to moderate renal impairement undergoing CAG and/or PCI, prehydration alone is less complicated and more cost-effective than a combination of IV NAC (at doses used) and hydration.

		C: 69 ± 9 *Sex:* *I1: 75% M* *I2: 86% M* *C: 89% M* *SCR (mmol/L)* *I1: 0.16 ± 0.03* *I2: 0.16 ± 0.03* *C: 0.15 ± 0.02* Groups comparable at baseline? Yes	procedure and once 2-4 hours after procedure (total dose 1200mg) Hydration iv: 0.9% saline 100ml/hour 2 hours before procedure and 5hours after procedure				
Sadineni, 2017	Type of study: randomized controlled trial Setting: Department of Nephrology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India Source of funding: not reported	<u>Inclusion criteria</u>: Age more than 30 years + Patients should have their serum creatinine ≥1.2 mg/dl on their most recent sample drawn within 3 months of planned procedure <u>Exclusion criteria</u>: Patients with acute renal failure, endstage renal disease requiring dialysis, intravascular administration of contrast material within previous 6 days, pregnancy, lactation, emergent coronary angiography, history of hypersensitivity reaction to contrast media, cardiogenic shock, pulmonary edema,	Describe intervention (treatment/procedure/test): NAC + NS: Group of patients who received NS and NAC	Describe control (treatment/procedure/test): Placebo + NS: Group of patients who received NS only	<u>Length of follow-up</u>: 48 hours <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN, defined as either a relative increase in serum creatinine from baseline of ≥25% or an absolute increase of ≥0.3 mg/dl (44.2 µmol/L) during days 1 and 2 NAC: 7/35 Placebo: 11/30 P > 0.05	Authors' conclusion: The major finding of this study was there was no significant difference between NAC and placebo in the prevention of contrast nephropathy.

		mechanical ventilator, parenteral use of diuretics, recent use of NAC, recent use of ascorbic acid, and use of metformin or NSAIDS within 48 h of procedure were excluded from the study. <u>N total at baseline</u>: NAC: 35 Placebo: 30 <u>Important prognostic factors[2]</u>: *For example* *age ± SD:* *NAC: 61 ± 11* *Placebo: 63 ± 12* *Sex:* *Group A: 77% M* *Group C: 87% M* Groups comparable at baseline? Yes					
Seyon, 2007	Type of study: randomized controlled trial Setting: emergency patients, one centre Country:	<u>Inclusion criteria</u>: 1) patients admitted with a diagnosis of acute coronary syndrome 2) scheduled for CAG and/or PCI 3) impaired renal function defined as: -calculated creatinine clearance <50ml/min or -sCr≥1.4mg/dL for males or	Describe intervention (treatment/procedure/test): 600mg NAC orally four doses in total (1 before procedure and 3 after every 12 hours)	Describe control (treatment/procedure/test): Iv hydration 0.45% saline1ml/kg/hour 4-6 hours before and 12 hours after procedure	<u>Length of follow-up</u>: 48 hours <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=increase in sCr >44µmol/L (0.5mg/dL) and/or 25% above baseline within 48 hours) I: 1/20 (5%) C: 2/20 (10%)	Authors' conclusion These results suggest that this cohort gained no added protection to renal function with the use of NAC

	Canada Source of funding: not reported	sCr≥1.3mg/dL for females 4) age ≥18 years <u>Exclusion criteria</u>: 1) hemodynamic instability requiring inotropic support 2) pregnancy 3) acute gastrointestinal disorder 4) Killip class III or IV or NYHA III or IV, or patients deemed by cardiologist unsuitable for iv hydration 5) known sensitivity to NAC 6) current treatment with theophylline or mannitol 7) dialysis therapy 8) participation in another study or use of experimental drugs <u>N total at baseline</u>: Intervention: 20 Control: 20 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I: 76 ± 6* *C: 75 ± 10* *Sex:* *I: 60% M* *C: 70% M* Groups comparable at	Iv hydration 0.45% saline1ml/kg/hour 4-6 hours before and 12 hours after procedure			p<0.05 No patients required dialysis therapy.	

		baseline? Yes					

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures**
2. **Provide data per treatment group on the most important prognostic factors [(potential) confounders]**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders**

CAG: coronary angiography; CECT: contrast-enhanced computed tomography; CI: confidence interval; CI-AKI: contrast-induced acute kidney injury; CIN: contrast induced nephropathy; iv: intravenous; NAC: N-acetylcysteine; NYHA: New York Heart Association; OR: odds ratio; PCI: percutaneous coronary intervention; SCr: serum creatinine

Search description

Database	Search terms	Total
Medline (OVID) 2005-juli 2015 English	1 exp Contrast Media/ or ((contrast adj3 iodine) or (contrast adj3 medi*)).ti,ab. (111910) 2 exp Kidney Diseases/ or (((kidney or renal) adj2 (disease* or injur* or failure*)) or nephropath* or (renal adj2 (insufficienc* or function* or disease* or failure*))).ti,ab. (535114) 3 1 and 2 (8902) 4 (((contrast* or ci) adj2 (nephropath* or 'kidney injury' or aki or nephrotoxicity)) or ciaki).ti,ab. (1951) 5 3 or 4 (9390) 6 limit 5 to (yr="2005 -Current" and (dutch or english)) (3922) 7 Acetylcysteine/ or ('acetyl cysteine' or acetylcysteine or (n adj1 acetyl*)).ti,ab. (71339) 8 6 and 7 (356) 9 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (245460) 10 8 and 9 (50) – 49 uniek 11 (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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1499747) 12 8 and 11 (184) 13 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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 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] (2196775) 14 8 and 13 (107) 15 12 not 10 (144) – 141 uniek 16 14 not (10 or 12) (23)	302
Embase (Elsevier)	'contrast induced nephropathy'/exp/dm_pc OR ((contrast* OR ci) NEAR/2 (nephropath* OR 'kidney injury' OR aki OR nephrotoxicity)):ab,ti OR ciaki:ab,ti OR ('contrast medium'/exp OR (contrast NEAR/3 iodine):ab,ti OR (contrast NEAR/3 medi*):ab,ti AND ('kidney disease'/exp OR 'kidney function'/exp OR (kidney NEAR/2 (disease* OR injur* OR failure*)):ab,ti OR nephropath*:ab,ti OR (renal NEAR/2 (insufficienc* OR function* OR disease* OR failure*)):ab,ti)) NOT 'conference abstract':it AND [english]/lim AND [embase]/lim AND [2005-2015]/py AND ('acetylcysteine'/exp/mj OR 'acetyl cysteine':ab,ti OR acetylcysteine:ab,ti OR (n NEAR/1 acetyl*):ab,ti) 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp))) (70) – 21 uniek AND '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 NOT 'conference abstract':it)) (171) – 56 uniek AND 'major clinical study'/de (25) – 12 uniek	

Appendices to Chapter 7.3

Evidence tables

Table: Exclusion after revision of full text

Author and year	Reason for exclusion
Albabtain, 2013	Included in systematic review by Sadat, 2013
Alexopoulos, 2010	No vitamin C administration in one of the treatment groups
Au, 2014	review, not specifically focussed on vitamin C (review of Sadat, 2013 of better quality and includes same literature)
Boscheri, 2005	Included in systematic review by Sadat, 2013
Briguori, 2006	review, not systematic
Briguori, 2007_1	vitamin C group not being compared to hydration only or no hydration group (does not comply with PICO)
Briguori, 2007_2	vitamin C group not being compared to hydration only or no hydration group (does not comply with PICO)
Bruerck, 2013	Included in systematic review by Sadat, 2013
De Bie, 2011	review, not systematic
Generali, 2012	review, not systematic
Itoh, 2005	review, not systematic
Jo, 2009	Included in systematic review by Sadat, 2013
Joannidis, 2007	review, not systematic
Kayan, 2012	Not a clinical study
McCullough, 2008	Letter to editor
McCullough, 2013	Letter to editor
Naziroglu, 2013	review, not specifically focussed on vitamin C (review of Sadat, 2013 of better quality and includes same literature)
Oudemans – van Straaten, 2005	review, not systematic
Pattharanitima, 2014	review, not systematic
Reiner, 2009	review, not systematic
Sadat, 2015	review, not systematic
Shakeryan, 2013	oral administration of vitamin C in combination with pentoxyfilline in treatment group (does not comply with PICO)
Sinert, 2007	more recent review by Sadat, 2013 available
Sinert, 2013	review, not systematic
Spargias, 2005	Included in systematic review by Sadat, 2013
Stacul, 2006	more recent review by Sadat, 2013 available
Wang, 2014	Article not found
Zhou, 2012	Included in systematic review by Sadat, 2013

Table of quality assessment for systematic reviews of RCTs and observational studies
Based on AMSTAR checklist (Shea et al.; 2007, BMC Methodol 7: 10;doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher et al 2009, PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Sadat, 2013	Yes	Yes	No	Yes	Not applicable	Yes	Yes	Yes	Yes

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs)**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table etc.)**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (e.g. Chi-square, I2)?**
8. **An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Risk of bias table for intervention studies (randomized controlled trials)

Research question:

Study reference (first author, publication year)	Describe method of randomisation[1]	Bias due to inadequate concealment of allocation?[2] (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?[4] (unlikely/likely/unclear)	Bias due to loss to follow-up?[5] (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?[6] (unlikely/likely/unclear)
Komiyama 2017	Not reported	Unclear	Unclear	Unclear	Unclear	Unlikely	Unlikely	Unclear
Dvoršak, 2013	Not reported	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear

1. **Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.**
2. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..**
3. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
5. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear**
6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

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

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Sadat, 2013 [individual study characteristics deduced from [1st author, year of publication]] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of [RCTs] *Literature search up to May 15th 2013* **A**: Sparglas, 2004 **B**: Boscheri, 2007 **C**: Jo, 2009 **D**: Zhou, 2011 **E**: Komiyama, 2011 **F**: Bruerck, 2011 **G**: Li, 2012 **H**: Albabtain, 2013 **I**:Hamdi, 2013 Study design: RCT [parallel] Setting and Country: Outpatients England and Pakistan Source of funding:	Inclusion criteria SR: 1) RCTs assessing the use of ascorbic acid in reducing CI-AKI compared with placebo or other pharmacological treatments in patients undergoing coronary angiography 2) route of administration of ascorbic acid: oral or intravenous or both 3) Incidence of CI-AKI (absolute increase in serum creatinine of ≥0.5 mg/dl (44µmol/L) or a relative increase of ≥25% from the baseline value after administration of contrast media during angiography) was reported as outcome measure Exclusion criteria SR: - *9 studies included* Important patient characteristics at baseline: *Number of patients; characteristics important to the research question and/or*	Describe intervention: **A**: Ascorbic acid, oral administration, 3g at least 2 hours after procedure, 2g night before and morning after procedure. Hydration with saline 50-125mg/hr IV from time of randomization to at least 6 hours after procedure **B**: 1g ascorbic acid orally 20 minutes before exposure to contrast medium, 500mL saline, 2 hours before and 500ml during angiography and subsequent 6 hours **C**: ascorbic acid, 3g (night before) and 2g morning of procedure; 2g night before and morning after procedure, oral administration, all doses 12 hours apart **D**: ascorbic acid, IV administration, 3g morning of procedure,	Describe control: **A**: placebo with IV hydration as in ascorbic acid arm **B**: placebo with IV hydration as in ascorbic acid arm **C**: 1200mG NAC orally 2x/daily on day of procedure and day before procedure **D**: IV saline hydration 1mg/kg/hour for 4 hours before and at least 12 hours after angiography **E**: IV saline hydration 1.5 – 2.5L **F**: placebo (per ascorbic acid dose) and IV saline (1/mg/kg/hour) for 12 hours before to 12 hours after contrast medium exposure **G**: IV saline hydration **H**: IV saline hydration	End-point of follow-up: Not reported For how many participants were no complete outcome data available? (intervention/control) Not reported	Outcome measure-1 Defined as. Risk of CI-AKI (risk ratio) Effect measure: relative risk [95% CI]: **A**: 0.46 (0.23 – 0.90) **B**: 1.55 (0.39 – 6.26) **C**: 3.65 (0.42 – 31.99) **D**: 1.35 (0.40 – 4.61) **E**: 0.25 (0.08 – 0.81) **F**: 0.76 (0.51 – 1.14) **G**: 1.14 (0.32 – 4.07) **H**: 0.46 (0.32 – 2.30) **I**: 0.49 (0.09 – 2.30) Pooled effect (random effects model): risk ratio: 0.672 [95% CI 0.466 to 0.969] favoring ascorbic acid Heterogeneity (I^2): 27% Outcome measure-2 Risk of publication bias Egger's regression intercept: 1.086 (95% CI: -2.57 – 4.74) df = 4 p=0.455	Facultative: Brief description of author's conclusion: Ascorbic acid provides effective nephroprotection against CI-AKI and may form a part of effective prophylactic pharmacological regiments. Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question: When studies on oral ascorbic acid administration and IV ascorbic acid administration were pooled separately, the ascorbic acid administration was as effective as control in prevention of CI-AKI. Level of evidence: GRADE (per comparison and

	Not reported	*for statistical adjustment (confounding in cohort studies); for example, age, sex, bmi, ...* <u>N,</u> **A**: 238 **B**: 143 **C**: 212 **D**: 174 **E**: 70 **F**: 520 **G**: 149 **H**: 243 **I**:202 Groups comparable at baseline? Unclear	oral 0.5g on the night of procedure and next morning (all doses 12 hours apart). IV saline hydration1mg/kg/hr for 4 hours before and at least 12 hours after angiography **E**: ascorbic acid, IV administration, 3g before procedure, 2g night and morning after procedure (12 hours apart). Saline hydration 1.5 – 2.5L **F**: ascorbic acid, IV administration **G**: ascorbic acid, IV 3g 2-4 hours before procedure and oral 1g on days 1 and 2 after procedure. IV saline hydration **H**: ascorbic acide, oral administration, 3g 2 hours before procedure, 2g after angiogram and 2g 24 hours after angiogram. IV saline 50-125 ml/hour from randomization until at least 6 hours after procedure **I**: ascorbic acid 3g 2 hours before procedure, 2g day after procedure and next day, mode of	**I**:IV saline hydration			outcome measure) including reasons for down/upgrading: For the outcome risk of CI-AKI the level of evidence was reduced to moderate, due to inconsistency of results.

			administration not reported				

Ascorbic acid = vitamin C;CI-AKI: contrast-induced acute kidney injury; CIN: contrast induced nephropathy; IV: intravenous; NAC: N-acetyl-cysteine; NR: not reported; RCT: randomised controlled trial

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series])1
This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy – otherwise the evidence table for studies of diagnostic test accuracy should be used.

Research question:

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Dvoršak, 2013	Type of study: randomized controlled trial Setting: not clear Country: Slovenia Source of funding: no funding	Inclusion criteria: 1) patients with stable serum creatinine levels (>107µmol/L / 1.2 mg/dL) 2) undergoing elective coronary angiography or angioplasty Exclusion criteria: 1) regular medication containing vitamin C 2) acute renal failure 3) end-stage renal disease 4) radiocontrast procedure in the last 3 months 5) cardiogenic shock 6) acute myocardial infarction N total at baseline: Intervention: 42 Control: 41 Important prognostic	Describe intervention (treatment/procedure/test): Ascorbic acid in 500mg capsules 3g orally before procedure 2g after the procedure in the evening and the next morning	Describe control (treatment/procedure/test): Placebo	Length of follow-up: 4 days Loss-to-follow-up: Intervention: 2/42 (5%) Reasons: lost to follow-up (?) Control: 0/41 (0%) Reasons: not applicable Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Contrast-induced nephropathy (+an increase in serum creatinine level >25% from baseline or increase of serum cystatin C levels >25%, measured 3-4 days after procedure) I: 2/40 C: 3/41 P=0.51	We found no statistically significant impact of ascorbic acid on the incidence of CIN in patients with chronic renal impairment undergoing coronary arteriography or angioplasty.

		factors[2]: *For example* *age ± SD:* *I: 71 ± 9* *C: 71 ± 9* *Sex:* *I: 78% M* *C: 68% M* Groups comparable at baseline? Yes					
Komiyama 2017	Type of study: randomized controlled trial Setting: hospital Country: Japan Source of funding: no funding	Inclusion criteria: patients with renal dysfunction undergoing elective angiography (including coronary angiography, aortography, and venography) or intervention (including percutaneous coronary intervention and endovascular treatment) with a catheter Exclusion criteria: 1) aged <20 years 2) pregnant or undergoing maintenance dialysis. 3) acute conditions such as acute myocardial infarction and unstable angina 3) severe cardiac failure (New York Heart Association class III or higher) 4) severe respiratory	Describe intervention (treatment/procedure/test): Sodium bicarbonate (20 mL=20 mEq; Meyron 84, Otsuka Pharmaceutical, Tokyo, Japan) and ascorbic acid (3 g) were given i.v. before the procedure. Ascorbic acid (2 g) was then administered after the procedure, followed by another 2 g of ascorbic acid 12 h later after the procedure; this group also received the same saline hydration protocol as the control	Describe control (treatment/procedure/test): The control group received 0.9% physiological saline 6–15 h before, and during, the procedure at a rate of 1.5 mL/kg/h. This rate was then increased to 2.5 mL/kg/h for 6 h after the procedure. The total amount of saline administered was 1,500–2,500 mL	Length of follow-up: 3 days Loss-to-follow-up: Intervention: None reported Reasons: not applicable Control: None reported Reasons: not applicable Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Contrast-induced nephropathy (+an increase in serum creatinine level >25% from baseline or increase of serum cystatin C levels >25%, measured 3 days after procedure) I: 6/211 C: 19/218 P=0.008	Use of i.v. sodium bicarbonate and ascorbic acid and a saline hydration protocol in patients with CKD undergoing elective procedures can prevent CIN more effectively than saline hydration alone.

		disease 5) undergone catheter procedures involving the use of a contrast agent within the previous 48 h N total at baseline: Intervention: 218 Control: 211 Important prognostic factors2: For example age ± SD: I: 73 ± 10 C: 74 ± 10 Sex: I: 79% M C: 82% M Groups comparable at baseline? Yes	group.				

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures**
2. **Provide data per treatment group on the most important prognostic factors [(potential) confounders]**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders**

Search description

Database	Search terms	Total
Medline (OVID) 1995-june English, Dutch	1 exp Contrast Media/ or ((contrast adj3 iodine) or (contrast adj3 medi*)).ti,ab. (110542) 2 exp Kidney Diseases/ or (((kidney or renal) adj2 (disease* or injur* or failure*)) or nephropath* or (renal adj2 (insufficienc* or function* or disease* or failure*))).ti,ab. (528935) 3 1 and 2 (8818) 4 (((contrast* or ci) adj2 (nephropath* or 'kidney injury' or aki or nephrotoxicity)) or ciaki).ti,ab. (1925) 5 3 or 4 (9301) 6 limit 5 to (yr="1995 -Current" and (dutch or english)) (5402) 9 "Ascorbic Acid"/ (36223) 10 ("vitamine C" or ascorbate or "ascorbic acid*").ti,ab. (36094) 11 9 or 10 (52727) 12 6 and 11 (32) 14 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (241238) 15 12 and 14 (8) – 7 uniek 16 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1475337) 17 12 and 16 (19) 18 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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 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] (2167237) 19 12 and 18 (8) 20 15 or 17 or 19 (21) 21 17 or 19 (19) not 15 (13)	113
Embase (Elsevier)	**'ascorbic acid'/exp OR 'vitamine c':ab,ti OR ascorbate:ab,ti OR (ascorbic NEAR/2 acid*):ab,ti AND ('contrast induced nephropathy'/exp/dm_pc OR ((contrast* OR ci) NEAR/2 (nephropath* OR 'kidney injury' OR aki OR nephrotoxicity)):ab,ti OR ciaki:ab,ti OR ('contrast medium'/exp OR (contrast NEAR/3 iodine):ab,ti OR (contrast NEAR/3 medi*):ab,ti AND ('kidney disease'/exp OR 'kidney function'/exp OR (kidney NEAR/2 (disease* OR injur* OR failure*)):ab,ti OR nephropath*:ab,ti OR (renal NEAR/2 (insufficienc* OR function* OR disease* OR failure*)):ab,ti))) NOT 'conference abstract':it AND ([dutch]/lim OR [english]/lim) AND [embase]/lim AND [1995-2015]/py** **'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT (animal* NOT human*) – 31 – 27 uniek** **'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 OR 'clinical study'/exp) – 79 – 66 uniek**	

Appendix 1
Additional meta-analyses

Figure 7.9 Meta-analysis also including the studies published in abstract form only

Study or Subgroup	vitamin C plus		hydration		Weight	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI
Albabtain 2013	2	57	5	66	4.4%	0.46 [0.09, 2.30]
Boscheri 2007	5	74	3	69	5.7%	1.55 [0.39, 6.26]
Brueck 2011	24	98	62	193	43.1%	0.76 [0.51, 1.14]
Dvorsak 2013	2	40	3	41	3.8%	0.68 [0.12, 3.88]
Komiyama 2011	5	78	4	71	6.8%	1.14 [0.32, 4.07]
Li 2012	3	35	12	35	7.9%	0.25 [0.08, 0.81]
Spargias 2004	11	118	23	113	21.0%	0.46 [0.23, 0.90]
Zhou 2011	6	82	4	74	7.3%	1.35 [0.40, 4.61]
Total (95% CI)		582		662	100.0%	0.68 [0.48, 0.96]
Total events	58		116			
Heterogeneity: Tau² = 0.03; Chi² = 7.85, df = 7 (P = 0.35); I² = 11%						
Test for overall effect: Z = 2.19 (P = 0.03)						

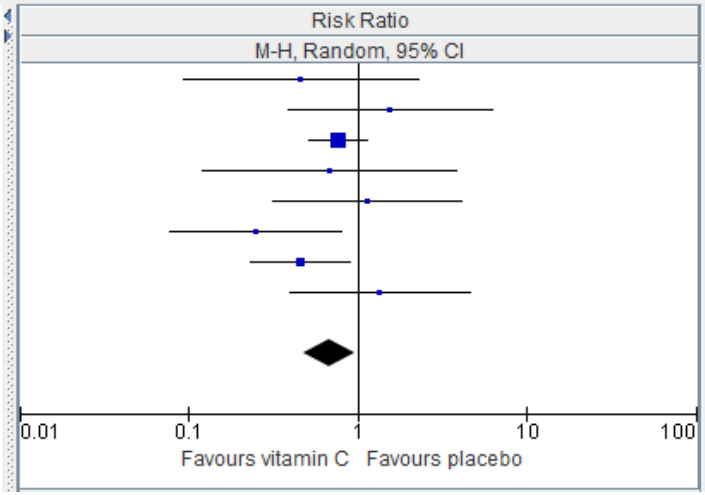
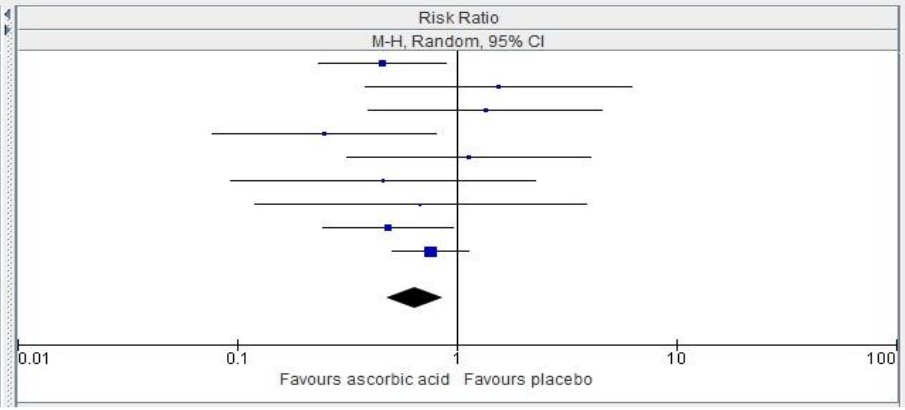


Figure 7.10 Meta-analysis including all RCTs on vitamin C (both impaired kidney function and kidney function not reported)

Study or Subgroup	ascorbic acid		placebo		Weight	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI
Spargias 2004	11	118	23	113	17.1%	0.46 [0.23, 0.90]
Boscher 2007	5	74	3	69	4.4%	1.55 [0.39, 6.26]
Zhou 2011	6	82	4	74	5.6%	1.35 [0.40, 4.61]
Komiyama 2011	3	35	12	35	6.1%	0.25 [0.08, 0.81]
Li 2012	5	78	4	71	5.2%	1.14 [0.32, 4.07]
Albabtain 2013	2	57	5	66	3.4%	0.46 [0.09, 2.30]
Dvorsak 2013	2	40	3	41	2.9%	0.68 [0.12, 3.88]
Hamdi 2013	11	107	20	95	16.6%	0.49 [0.25, 0.97]
Bruerck 2013	24	98	62	193	38.6%	0.76 [0.51, 1.14]
Total (95% CI)		689		757	100.0%	0.65 [0.48, 0.87]
Total events	69		136			
Heterogeneity: Tau² = 0.02; Chi² = 8.67, df = 8 (P = 0.37); I² = 8%						
Test for overall effect: Z = 2.88 (P = 0.004)						



Appendices to Chapter 7.4

Evidence Tables

Table: exclusion after examination of full text

Author and year	Reasons for exclusion
Aspelin, 2014	Exam questions, not an original article
Baris, 2013	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Cirit, 2006	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Del Veccio	Narrative review
Diogo, 2010	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Duan, 2015	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination but started, with the hypothesis that this will prevent kidney injury)
Goo, 2014	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Gu, 2013	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination but started, with the hypothesis that this will prevent kidney injury)
Gu, 2015	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination but started, with the hypothesis that this will prevent kidney injury)
Jo, 2015	Only abstract available (full tekst nogmaals aangevraagd bij Sanne, aan de hand hiervan alsnog inclusie mogelijk)
Kalyesubula, 2014	Narrative review
Kellum, 2001	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Kiski, 2010	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Lapi, 2014	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Li, 2011	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Li, 2012	Narrative review
Li, 2012b	Only abstract available (full tekst nogmaals aangevraagd bij Sanne, aan de hand hiervan alsnog inclusie mogelijk)
Marenzi, 2012	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination but started, with the hypothesis that this will prevent kidney injury)
Mauer, 2002	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination but started, with the hypothesis that this will prevent kidney injury)
Oguzhan, 2013	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination but started, with the hypothesis that this will prevent kidney injury)
Onuigbo, 2008	No control group
Onuigbo, 2009	Narrative review
Onuigbo, 2012	Narrative review
Onuigbo, 2015	Editorial comment, not an original article
Patel, 2011	Narrative review
Peng, 2015	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination but started, with the hypothesis that this will prevent kidney injury)
Rim, 2012	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination but started, with the hypothesis that this will prevent kidney injury)
Rim, 2013	Erratum of Rim, 2012; not an original article
Ryan, 2008	Narrative review

Saudan, 2008	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination but started, with the hypothesis that this will prevent kidney injury)
Schetz, 2004	Narrative review
Shehata, 2015	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Shemirani, 2012	Patients with normal kidney function
Spatz, 2012	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Umruddin, 2012	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Wolak, 2013	Patients with normal kidney function
Wu, 2015	Does not fulfill selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Zhou, 2013	Narrative review

Risk of bias table for intervention studies (randomized controlled trials)
Research question:

Study reference (first author, publication year)	**Describe method of randomisation**[1]	**Bias due to inadequate concealment of allocation?**[2] (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?**[4] (unlikely/likely/unclear)	**Bias due to loss to follow-up?**[5] (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?**[6] (unlikely/likely/unclear)
Bainey, 2015	Permuted block-randomization; computerized intractive voice-response system	Unlikely	Unlikelu	Unclear	Unclear	Unlikely	Unclear	Unlikely
Rosenstock, 2008	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

1. **Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.**
2. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..**
3. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
5. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear**
6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series])1
This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy – otherwise the evidence table for studies of diagnostic test accuracy should be used.

Research question:

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Bainey, 2015	Type of study: Randomized controlled trial (pilot) Setting: outpatients and inpatients Country: Canada Source of funding: both commercial and non-commercial	Inclusion criteria: 1) presented for cardiac catheterization 2) using an ACEi or ARB 3) moderate chronic kidney disease (≥1.7 mg/dL within 3 months or ≥1.5 within one week of cardiac catheterisation) Exclusion criteria: 1) end-stage renal disease 2) emergency cardiac catheterisation with insufficient time to hold ACEi 3) pulmonary oedema N total at baseline: 208 Intervention: 106	Describe intervention (treatment/procedure/test): Angiotensin II blockade medication was stopped at least 24 hours prior to catheterisation and restarted after up to 96 hours after. Intravenous normal saline at 3 mL/kg/hour for at least an hour before contrast injection, intravebous normal saline at 1 mL/kg/hour during contrast exposure and 6 hours after the procedure or until discharge.	Describe control (treatment/procedure/test): No discontinuation of angiotensin II blockade medication Intravenous normal saline at 3 mL/kg/hour for at least an hour before contrast injection, intravebous normal saline at 1 mL/kg/hour during contrast exposure and 6 hours after the procedure or until discharge.	Length of follow-up: 72±24 hours Loss-to-follow-up: not reported Incomplete outcome data: not reported	Outcome measures and effect size (include 95%CI and p-value if available): Mean serum creatinine change I: 0.1±0.3 C: 0.3±0.5 P=0.03 Contrast induced AKI: I: 10.9% C: 18.4% HR: 0.59, 95% CI: 0.30 – 1.19, p=0.16 Mortality: I: 0 (0%) C: 1 (1%) Ischemic stroke: I: 0 (0%) C: 1 (1%) Rehospitalization	Contrast induced AKI defined as an absolute rize in serum creatinine of ≥25% (44µmol/L) from baseline and/or a relative rise of serum creatinine of ≥25% compared with baseline at any time between 48 and 96 hours post procedure.

		Control: 102 Important prognostic factors[2]: *For example* *age ± SD:* *I: 73 ± 9* *C: 72 ± 8* *Sex:* *I: 74% M* *C: 73 % M* Groups comparable at baseline? yes				for cardiovascular cause: I: 0 (0%) C: 3 (2%)	
Rosenstock, 2008	Type of study: Randomized controlled trial Setting: unclear Country: unclear Source of funding: unclear	Inclusion criteria: 1) patients undergoing coronary angiography 2) chronic use (>2 months) of ACE-inhibitor Exclusion criteria: unclear N total at baseline: Intervention: 107 Control: 113 ACE-naïve patients: 68 Important prognostic	Describe intervention (treatment/procedure/test): Discontinuation of ACE inhibitor use Morning of procedure up to 24 hours after coronary angiography Patients were hydrated based on the institution's policies and medications such as diuretics and metformin were held prior to procedure	Describe control (treatment/procedure/test): 1) No Discontinuation of ACE inhibitor use around coronary angiography 2) ACE-inhibitor naïve patients undergoing coronary angiography Patients were hydrated based on the institution's policies and medications such as diuretics and metformin were held prior to procedure	Length of follow-up: 24 hours Loss-to-follow-up: unclear Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe) Incomplete	Outcome measures and effect size (include 95%CI and p-value if available): Incidence of CIN ACE-inhibitors discontinued: 3.7% ACE-inhibitors not discontinued: 6.2% ACE-inhibitor naïve group: 6.3% P=0.66	Measurements of creatinine 24 hours post-procedure; various ACE-inhibitor subgroups not compared due to small sample size.

		factors[2]: unclear *For example* *age ± SD:* *I:* *C:* *Sex:* *I: % M* *C: % M* Groups comparable at baseline? Incidence of diabetes and hypertension was significantly lower in the ACE-naïve group			outcome data: unclear Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe)		
1st author, year of publication	Type of study: Setting: Country: Source of funding:	Inclusion criteria: Exclusion criteria: N total at baseline: Intervention: Control: Important prognostic factors[2]: *For example* *age ± SD:* *I:* *C:* *Sex:* *I: % M*	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	Length of follow-up: Loss-to-follow-up: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe) Incomplete outcome	Outcome measures and effect size (include 95%CI and p-value if available):	

		C: % M Groups comparable at baseline?			data: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe)		
1st author, year of publication	Type of study: Setting: Country: Source of funding:	Inclusion criteria: Exclusion criteria: N total at baseline: Intervention: Control: Important prognostic factors[2]: *For example age ± SD:* *I:* *C:* *Sex:* *I: % M* *C: % M* Groups comparable at baseline?	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	Length of follow-up: Loss-to-follow-up: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe) Incomplete outcome data: Intervention: N (%) Reasons (describe) Control: N (%) Reasons	Outcome measures and effect size (include 95%CI and p-value if available):	

					(describe)		

ACEi: angiotensin converting enzyme inhibitor; AKI: acute kidney injury; ARB: angiotensin receptor blocker; CIN: contrast induced nephropathy; HR: hazard ratio

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures**
2. **Provide data per treatment group on the most important prognostic factors [(potential) confounders]**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders**

Search terms

Database	Search terms	Total
	1 exp Contrast Media/ or ((contrast adj3 iodine) or (contrast adj3 medi*)).ti,ab. (112523) 2 exp Kidney Diseases/ or (((kidney or renal) adj2 (disease* or injur* or failure*)) or nephropath* or (renal adj2 (insufficienc* or function* or disease* or failure*))).ti,ab. (537836) 3 (((contrast* or ci) adj2 (nephropath* or 'kidney injury' or aki or nephrotoxicity)) or cin or ciaki).ti,ab. (9122) 4 1 and 2 (8979) 10 3 or 4 (16547) 12 exp "Angiotensin Receptor Antagonists"/ (18363) 13 exp Angiotensin-Converting Enzyme Inhibitors/ (40094) 14 exp Diuretics/ (72995) 15 exp Anti-Inflammatory Agents, Non-Steroidal/ (164802) 16 12 or 13 or 14 or 15 (279958) 17 ((Angiotensin* adj3 (Antagonist or Inhibitor* or blocker*)) or Diuretic* or "Non-Steroidal Anti-Inflammatory Agent*" or NSAID* or (nephrotoxic adj3 medic*)).ti,ab. (74424) 18 12 or 13 or 14 or 15 or 17 (307695) 19 10 and 18 (641) 20 limit 19 to (yr="2000 -Current" and (dutch or english)) (266) 21 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (249387) 22 20 and 21 (26) - 25 uniek 23 (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$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1512514) 24 20 and 23 (75) 25 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.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 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] (2216587) 26 20 and 25 (81) 27 24 or 26 (128) 28 27 not 22 (109) – 107 uniek	320
	'contrast induced nephropathy'/exp/dm_pc OR ((contrast* OR ci) NEAR/2 (nephropath* OR 'kidney injury' OR aki OR nephrotoxicity)):ab,ti OR ciaki:ab,ti OR ('contrast medium'/exp OR (contrast NEAR/3 iodine):ab,ti OR (contrast NEAR/3 medi*):ab,ti AND ('kidney disease'/exp OR 'kidney function'/exp OR (kidney NEAR/2 (disease* OR injur* OR failure*)):ab,ti OR nephropath*:ab,ti OR (renal NEAR/2 (insufficienc* OR function* OR disease* OR failure*)):ab,ti)) AND ('angiotensin receptor antagonist'/exp/mj OR 'dipeptidyl carboxypeptidase inhibitor'/exp/mj OR 'diuretic agent'/exp/mj OR 'nonsteroid antiinflammatory agent'/exp/mj OR (angiotensin* NEAR/3 (antagonist OR inhibitor* OR blocker*)):ab,ti OR diuretic*:ab,ti OR 'non-steroidal anti-inflammatory agent':ab,ti OR 'non-steroidal anti-inflammatory agents':ab,ti OR nsaids:ab,ti OR (nephrotoxic NEAR/3 medic*):ab,ti) AND ([dutch]/lim OR [english]/lim) AND [embase]/lim AND [2000-2015]/py 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp)) (38) – 26 uniek '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) NOT 'conference abstract':it OR 'clinical study'/exp NOT 'conference abstract':it (225) – 162 uniek	

Appendices to Chapter 7.5

Evidence tables

Table: Exclusion after revision of full text

Author and year	Reason for exclusion
Chang, 2013	Does not fulfill selection criteria
Choi, 2014	Does not fulfill selection criteria
Cruz, 2006	Does not fulfill selection criteria
Cruz, 2008	Does not fulfill selection criteria
Deray, 2006	Does not fulfill selection criteria
Frank, 2003	Already included in systematic review Cruz, 2012
Furukawa, 1996	Does not fulfill selection criteria
Gabutti, 2003	Does not fulfill selection criteria
Ghani, 2011	Does not fulfill selection criteria
Hsieh, 2005	Already included in systematic review Cruz, 2012
Huber, 2002	Does not fulfill selection criteria
Joannidis, 2010	Does not fulfill selection criteria
Lee, 2007	Already included in systematic review Cruz, 2012
Lehnert, 1998	Already included in systematic review Cruz, 2012
Marenzi, 2003	Already included in systematic review Cruz, 2012
Marenzi, 2004	Does not fulfill selection criteria
Marenzi, 2006	Already included in systematic review Cruz, 2012
Marenzi, 2007	Does not fulfill selection criteria
Moon, 1995	Does not fulfill selection criteria
Ono, 2004	Does not fulfill selection criteria
Reinecke, 2007	Already included in systematic review Cruz, 2012
Schindler, 2001	Does not fulfill selection criteria
Shinoda, 2002	Does not fulfill selection criteria
Song, 2010	Does not fulfill selection criteria
Song, 2011	Does not fulfill selection criteria
Sterner, 2000	Already included in systematic review Cruz, 2012
Vogt, 2001	Already included in systematic review Cruz, 2012

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea et al.; 2007, BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher et al 2009, PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Cruz, 2012	Yes	Yes	No	Yes	No	Yes	Yes	No	No

10. **Research question (PICO) and inclusion criteria should be appropriate and predefined**
11. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched**
12. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons**
13. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported**
14. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs)**
15. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table etc.)**
16. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (e.g. Chi-square, I^2)?**
17. **An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
18. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Risk of bias table for intervention studies (randomized controlled trials)
Research question:

Study reference (first author, publication year)	**Describe method of randomisation**[1]	**Bias due to inadequate concealment of allocation?**[2] (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?**[4] (unlikely/likely/unclear)	**Bias due to loss to follow-up?**[5] (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?**[6] (unlikely/likely/unclear)
Spini, 2013	Not randomised	Unlikely	Unclear	Unclear	Unclear	Unlikely	Unlikely	Unclear

13. **Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.**
14. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..**
15. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
16. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
17. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear**
18. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)
Evidence table for systematic review of RCTs and observational studies (intervention studies)
Research question:

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Cruz, 2012 individual study characteristics deduced from [1st author, year of publication PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of RCTs / cohort studies *Literature search up to March 2011* **A**: Lee, 2007 **B**: Reinecke, 2007 **C**: Marenzi, 2006 **D**: Hsieh, 2005 **E**: Marenzi, 2003 **F**: Frank, 2003 **G**: Gabutti, 2003 **H**: Vogt, 2001 **I**: Sterner, 2000 **J:** Berger, 2001 **K:** Lehnert, 2008 <u>Study design</u>: **A**: Randomized trial **B**: Randomized trial **C**: Randomized trial **D**: Observational **E**: Randomized trial **F**: Randomized	Inclusion criteria SR: 1) studies that ecaluated the use of periprocedural renal replacement therapy (RRT) for the prevention of radiocontrast induced nephropathy (RCIN) as compared with standard medical treatment (SMT) 2) 10 or more human subjects 3) primary outcome: RCIN (sCR ≥0.5mg/dL / 44 umol/L); secondary outcomes: need for temporary acute RRT, need for permanent RRT, long-term changes in renal function, death Exclusion criteria SR: *11 studies included* <u>Important patient characteristics at baseline</u>: *Number of patients; characteristics important to the research question and/or for statistical adjustment (confounding in cohort*	Describe intervention: **A**: hemodialysis (HD) **B**: HD **C**: HD **D**: HD **E**: HD **F**: HD **G**: HD **H**: HD **I**: Hemofiltration (HF) **J:** HF **K:** Hemodiafiltration	Describe control: For all studies: Standard medical therapy, depending on hospital either pre-hydration or pre- and posthydration	<u>End-point of follow-up</u>: Not reported <u>For how many participants were no complete outcome data available?</u> Not reported	<u>Outcome measure-1</u> Defined as RCIN Reported for CKD stage 4-5 patients only Effect measure: RR [95% CI]: **J:** 3.43 (0.45 – 25.93) **G:** 1.56 (0.66 – 3.72) **D**: 0.33 (0.01 – 7.72) **E:** 0.12 (0.05 – 0.32) **C:** 0.48 (0.27 – 0.88) **I:** 1.70 (0.59 – 4.90) **H:** 1.27 (0.80 – 2.01) Pooled effect (random effects model): 0.81 [95% CI 0.37 to 1.76] favoring RRT. Heterogeneity (I^2): 79% <u>Outcome measure-2</u> Risk for acute RRT HDF/HF **G:** 2.89 (0.12 – 67.75) **E:** 0.14 (0.03 – 0.58) **C:** 0.16 (0.05 – 0.55) Pooled effect (random effects model): 0.22 [95% CI 0.06 to 0.74] favoring RRT.	<u>Facultative</u>: Brief description of author's conclusion: In this updated meta-analysis periproceural RRT did not decrease the incidence of RCIN compared with SMT. HD appears to actually increase RCIN risk. Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question: In our own literature analysis the observational studies were excluded from the systematic review and only the RCTs with patients CKD stage 4-5 were included. Level of evidence: GRADE Low to Very low for most studies due to high risk of bias in several studies, wide confidence intervals (imprecision) and

	trial **G**: Observational **H**: Randomized trial **I**: Randomized trial **J:** Randomized trial **K:** Randomized trial <u>Setting and Country</u>: Italy <u>Source of funding:</u> No funding	*studies); for example, age, sex, bmi, ...* <u>Number of patients , age (years)</u> **A**: 82; 65-66 **B**: 424; 67-68 **C**: 92; 71-72 **D**: 40; 66-69 **E**: 114; 69 **F**: 17; 58-67 **G**: 49; 70 **H**: 113; 69-70 **I**:32; 65-72 **J:** 15; 62-68 **K:** 30; 60-63 <u>*Sex*</u>*: not reported* Groups comparable at baseline? Unclear				Heterogeneity (I^2): 36% HD **A:** 0.07 (0.01 – 0.49) **B:** 2.05 (0.29 – 14.41) **H:** 2.81 (0.70 – 10.06) Pooled effect (random effects model): 0.78 [95% CI 0.07 to 8.43] favoring RRT. Heterogeneity (I^2): 83% <u>Outcome measure-3</u> Risk for chronic RRT HDF/HF **E:** 0.32 (0.03 – 3.00) HD F: 1.43 (0.26 – 7.86) D: 1.33 (0.34 – 5.21) A: 0.09 (0.00 – 1.52) H: 2.11 (0.20 – 22.61) Pooled effect (random effects model): 0.87 [95% CI 0.33 to 2.29] favoring RRT. Heterogeneity (I^2): 19% <u>Outcome measure-4</u> Mortality Not reported per study. Pooled analysis for 5 studies. I: 2.6%	heterogeneity of included studies

						C: 3.7% RR: 0.65, 95% CI: 0.17 – 2.49	

CIN: contrast induced nephropathy; NAC: N-acetyl-cysteine; NR: not reported

Evidence table for intervention studies (randomized controlled trials and non-randomized *observational* studies [cohort studies, case-control studies, case series])[1]
This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy – otherwise the evidence table for studies of diagnostic test accuracy should be used.

Research question:

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Spini, 2013	Type of study: prospective controlled trial Setting: cardiac stepdown Country: Italy Source of funding: not reported	Inclusion criteria: patients admitted to the cardiac stepdown at the participating hospital -eGFR <30mL/min -needed to be submitted to percutaneous intervention Exclusion criteria: - N total at baseline: 46 Intervention: 25 Control: 21	Describe intervention (treatment/procedure/test): Continuous renal replacement therapy (CRRT) at least 6 hours before and 24 hours after contrast medium administration	Describe control (treatment/procedure/test): CRRT only after percutaneous intervention	Length of follow-up: Creatinine levels – 72 hours Mortality 12 months, 18 months Loss-to-follow-up: not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Contrast induced nephropathy (CIN): I: 0/25 (0%) C: 13/21 (62%) p-value not reported Worsening renal failure: I: 3/25 (12%) C: 9/25 (43%) p-0.042 Dialysis: I: 2/25 (8%) C: 9/21 (19%) P=0.50 Long-term mortality: I: 4/25 (16%) I: 12/21 (57%)	A limitation of using PC-AKI / CIN as an endpoint, is that creatinine, which forms the base of the PC-AKI definition, is removed by RRT. However, creatinine is removed by CRRT.

		<u>Important prognostic factors</u>[2]: *For example age ± SD:* *I: 73 ± 11* *C: 74 ± 8* *Sex:* *I: 84% M* *C: 67% M* Groups comparable at baseline? Yes				P0.009 Cardiovascular deaths: I: 0/25 (0%) C: 5/21 (24%) p-value not reported	

Notes:

5. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures**
6. **Provide data per treatment group on the most important prognostic factors [(potential) confounders]**
7. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls**
8. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders**

Search description

Database	Search terms	Total
Medline (OVID) 1995-okt. 2015 English	1 exp Contrast Media/ or ((contrast adj3 iodine) or (contrast adj3 medi*)).ti,ab. (113850) 2 exp Kidney Diseases/ or (((kidney or renal) adj2 (disease* or injur* or failure*)) or nephropath* or (renal adj2 (insufficienc* or function* or disease* or failure*))).ti,ab. (543550) 3 (((contrast* or ci) adj2 (nephropath* or 'kidney injury' or aki or nephrotoxicity)) or cin or ciaki).ti,ab. (9272) 4 1 and 2 (9076) 5 (((contrast* or ci) adj2 (nephropath* or 'kidney injury' or aki or nephrotoxicity)) or cin or ciaki).ti,ab. (9272) 6 4 or 5 (16764) 7 exp Hemofiltration/ or exp Renal Dialysis/ (103123) 8 (Hemofiltrat* or Haemofiltrat* or Haemodiafiltrat* or Hemodiafiltrat* or Dialysis or hemodialysis or haemodialysis).ti,ab. (130690) 9 7 or 8 (153364) 10 6 and 9 (918) 11 (prophyla* or prevent*).ti,ab. or pc.fs. (1907859) 12 10 and 11 (356) 13 limit 12 to (english language and yr="1995 -Current") (302) 14 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (254827) 15 13 and 14 (59) 16 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).mp. or comparative study.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/) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2605774) 17 13 and 16 (149) 18 The prevention of radiocontrast-agent-induced nephropathy by hemofiltration.m_titl. (1) 19 Effects of two different treatments with continuous renal replacement therapy in patients with chronic renal dysfunction submitted to coronary invasive procedures.m_titl. (1) 20 "Renal replacement therapies for prevention of radiocontrast-induced nephropathy: a systematic review.".m_titl. (1) 21 18 or 19 or 20 (3) 22 15 or 17 (166) 23 21 and 22 (3) 24 17 not 15 (107) 25 remove duplicates from 15 (56) 26 remove duplicates from 24 (104)	194
Embase (Elsevier)	'contrast induced nephropathy'/exp/dm_pc OR ((contrast* OR ci) NEAR/2 (nephropath* OR 'kidney injury' OR aki OR nephrotoxicity)):ab,ti OR ciaki:ab,ti OR ('contrast medium'/exp OR (contrast NEAR/3 iodine):ab,ti OR (contrast NEAR/3 medi*):ab,ti AND ('kidney disease'/exp OR 'kidney function'/exp OR (kidney NEAR/2 (disease* OR injur* OR failure*)):ab,ti OR nephropath*:ab,ti OR (renal NEAR/2 (insufficienc* OR function* OR disease* OR failure*)):ab,ti)) AND [english]/lim AND [1995-2015]/py AND ('hemofiltration'/exp/mj OR 'hemodialysis'/exp/mj OR hemofiltrat*:ab,ti OR haemofiltrat*:ab,ti OR haemodiafiltrat*:ab,ti OR hemodiafiltrat*:ab,ti OR hemodialysis:ab,ti OR haemodialysis:ab,ti) AND ('prophylaxis'/exp OR prophyla*:ab,ti OR prevent*:ab,ti OR prevention:lnk) 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp)) (26) – 9 uniek AND ('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) NOT 'conference abstract':it - (57) – 25 uniek	

Appendices to Chapter 8

Evidence tables

Table: Exclusion of article after examination of full tekst.

Author and year	Reason for exclusion
Aronson, 2007	Does not meet selection criteria
Baerlocher, 2013	Review, not systematic
Blickle, 2007	Does not meet selection criteria
Bloomgarten, 1996	Does not meet selection criteria
Boscheri, 2007	Does not meet selection criteria
Chan, 1999	Does not meet selection criteria
Chong, 2004	Does not meet selection criteria
Cicero, 2012	Does not meet selection criteria
Dawson, 2002	Does not meet selection criteria
Dichtwald, 2011	Case series, no control group
Douros, 2015	Does not meet selection criteria
Elder, 2003	Does not meet selection criteria
Erley, 2006	Does not meet selection criteria
Goergen, 2010_1	Does not meet selection criteria
Gomez-Herrerp, 2013	Does not meet selection criteria
Gupta, 2002	Does not meet selection criteria
Hammond	Does not meet selection criteria
Heikkinen, 2007	Does not meet selection criteria
Heupler, 1998	Does not meet selection criteria
Hoste, 2013	Does not meet selection criteria
Jain, 2008	Included in systematic review Goergen, 2010
Jones, 2003	Does not meet selection criteria
Kdoqi, 2007	Does not meet selection criteria
Khurana, 2010_1	Review, not systematic
Khurana, 2010_2	Letter to editor
Klepser, 1997	Does not meet selection criteria
Koc, 2013	Does not meet selection criteria
Lalau, 2001	Systematic review, however more recent systematic (Georgen, 2010) present and included in literature summary
Landewe-Cleuren, 2000	Review, not systematic
Leow, 2015	Does not meet selection criteria
Longeran, 2008	Does not meet selection criteria
McCartney, 1999	Systematic review, however more recent systematic (Georgen, 2010) present and included in literature summary
Millican, 2004	Does not meet selection criteria
Morcos, 2001	Does not meet selection criteria
Morcos, 2005	Does not meet selection criteria
Nawaz, 1998	Included in systematic review Goergen, 2010
Nolan, 1997	Does not meet selection criteria
Parra, 2004	No control group.
Pond, 1996	Does not meet selection criteria
Quasny, 1997	Does not meet selection criteria
Radwan, 2011	Does not meet selection criteria
Rakovac, 2005	Does not meet selection criteria
Rasuli, 1998_1	Does not meet selection criteria
Rasuli, 1998_2	Does not meet selection criteria
Safadi, 1996	Does not meet selection criteria
Sayer, 2006	Letter to the editor
Schweiger, 2007	Does not meet selection criteria
Senior, 2012	Does not meet selection criteria
Setter, 2003	Does not meet selection criteria
Stacul, 2006	Does not meet selection criteria
Stacul, 2011	Guideline tekst, not an original article

Thompson, 2000	Does not meet selection criteria
Thomsen, 2003	Guideline tekst, not an original article
Thomsen, 2010	Does not meet selection criteria
Thomson 2010	Does not meet selection criteria
Tonolini, 2012	Does not meet selection criteria
Tzakias, 2013	Does not meet selection criteria
Tzakias, 2014	Does not meet selection criteria
Van Dijk, 2008	Does not meet selection criteria
Widmark, 2007	Does not meet selection criteria

Table of quality assessment for systematic reviews of RCTs and observational studies
Based on AMSTAR checklist (Shea et al.; 2007, BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher et al 2009, PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Goergen, 2010	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	No	No

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs)**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table etc.)**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (e.g. Chi-square, I2)?**
8. **An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Risk of bias table for intervention studies (randomized controlled trials)
Evidence table for systematic review of RCTs and observational studies (intervention studies)

Research question:

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Goergen, 2010	SR and meta-analysis of [RCTs	Inclusion criteria SR: 1) English language publication	Describe intervention:	Describe control:	End-point of follow-up:	Outcome measure-1 Defined as presence of	Facultative:

[individual study characteristics deduced from [1st author, year of publication] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	/ cohort / case-control studies] *Literature search up to March 2009* **A**: Nawaz, 1998 **B**: MacCartney, 1999 **C**: Stades, 2004 **D**: Jain, 2008 <u>Study design</u>: RCT [parallel / cross-over], cohort [prospective / retrospective], case-series, case-control **A**: case-series **B**: summary of case-reports **C**: summary of case-reports **D**: case report <u>Setting and Country</u>: Australia, in- and outpatiennts <u>Source of funding:</u> Not reported	2) administration of iodinated contrast medium in adult patients who were tacing metformin 3) lactic acidosis was outcome measure Exclusion criteria SR: 1) studies in children (<18 years) 2) procedures in which administration of contrast medium was not used 3) lactic acidosis was not one of the outcomes assessed 4) publications that were letters, narratives, editorials, reviews based on only expert opinion, draft reports *4 studies included* <u>Important patient characteristics at baseline</u>: <u>N, mean age</u> **A**: 33, not reported B: 18, not reported **C**: 47, not reported **D: 1,** not reported *<u>Sex</u>:* **A**: not reported **B**: not reported **C**: not reported D: not reported	**A**: metformin and undergoing angiography **B**: patients who had metformin-associated lactic acidosis after use of intravenous iodinated contrast medium **C**: patients who had metformin-associated lactic acidosis, 26% of them received contrast medium prior **D**: metformin-associated lactic acidosis,	**A**: not applicable **B**: not applicable **C**: not applicable **D**: not applicable	**A**: not reported **B**: not reported **C**: not reported **D**: not reported <u>For how many participants were no complete outcome data available?</u> (intervention/control) **A:** not reported **B**: not reported **C**: not reported **D**: not reported	metformin associated lactic acidosis (MALA), or relation between MALA and iodinated contrast medium administration Effect measure: RR, RD, mean difference [95% CI]: **A:** 4 patients died (2 attributed to acute renal failure and lactic acidosis), in 29 patients with normal renal function no change was observed after procedure **B**: in 16-17 out of 18 cases renal dysfunction or other contra-indication was present **C**: 25% of cases had intravascular contrast medium administered **D**: metformin-associated lactic acidosis, developed in patient with normal renal function Pooled effect (random effects model / fixed effects model): No pooling was possible due to heterogeneity of included studies	Brief description of author's conclusion: It is not clear whether cessation of metformin in patient undergoing intravascular contrast administration for radiological examination is effective for decreasing the risk of lactic acidosis and hyperglycemia. Level of evidence: GRADE: All included studies had a very low quality of evidence (summaries of case-reports, case-series, case-report) -no studies with control group For study C (stades, 2004) contrast medium was administered in 26% of the cases.

		Impaired renal function: A; 4/33 (12%) B:16/18 (89%) (unclear if this is correct number) C: not reported D: 0/1 (0%) Groups comparable at baseline? Not applicable (no control group)					

Search description

Database	Search terms	Total
Medline (OVID) 1995-now English Dutch	1 exp Contrast Media/ or ((contrast adj3 iodine) or (contrast adj3 medi*)).ti,ab. (111686) 2 exp Kidney Diseases/ or (((kidney or renal) adj2 (disease* or injur* or failure*)) or nephropath* or (renal adj2 (insufficienc* or function* or disease* or failure*))).ti,ab. (534205) 3 1 and 2 (8890) 4 (((contrast* or ci) adj2 (nephropath* or 'kidney injury' or aki or nephrotoxicity)) or ciaki).ti,ab. (1942) 5 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (244003) 6 3 or 4 (9377) 7 limit 6 to (yr="1995 -Current" and (dutch or english)) (5451) 8 Metformin/ or (metformin* or glucophage).ti,ab. (12587) 9 7 and 8 (53) – 52 uniek	202
	'contrast induced nephropathy'/exp/dm_pc OR ((contrast* OR ci) NEAR/2 (nephropath* OR 'kidney injury' OR aki OR nephrotoxicity)):ab,ti OR ciaki:ab,ti OR ('contrast medium'/exp OR (contrast NEAR/3 iodine):ab,ti OR (contrast NEAR/3 medi*):ab,ti AND ('kidney disease'/exp OR 'kidney function'/exp OR (kidney NEAR/2 (disease* OR injur* OR failure*)):ab,ti OR nephropath*:ab,ti OR (renal NEAR/2 (insufficienc* OR function* OR disease* OR failure*)):ab,ti)) NOT 'conference abstract':it AND ([dutch]/lim OR [english]/lim) AND [embase]/lim AND [1995-2015]/py AND ('metformin'/exp OR metformin*:ab,ti OR glucophage:ab,ti) (191) – 150 uniek	