Appendices to Guideline Safe Use of Contrast Media

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2. PC-AKI

2.1 Definitions, terminology and clinical course

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2.2 Risk stratification and stratification tools

Tables of excluded studies

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

Author and year	Reasons for exclusion
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, 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	Reasons of exclusion
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 text: Measurement instruments for PC-AKI risk

Author and year	Reasons for exclusion
Aguiar, 2008	Letter to the editor
Akgullu, 2015	Does not fulfil selection criteria, no risk score is validated/developed
Balemans, 2012	Does not fulfil 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 fulfil selection criteria, no risk score is validated/developed
Crit, 2006	Does not fulfil 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 fulfil selection criteria, no risk score is validated/developed
Kim, 2011	Does not fulfil selection criteria, no risk score is validated/developed
Kooiman, 2010	Does not fulfil selection criteria, no risk score is validated/developed
Kowalczyk, 2007	Does not fulfil selection criteria, no risk score is validated/developed
Lepanto, 2011	Narrative review
Li, 2013	The diagnostic properties of a laboratory analysis (anaemia) 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 creatinine 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 fulfil 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 fulfil 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 fulfil 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

Evidence tables

Table of quality assessment for systematic reviews

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/not applicable	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

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 assignment influences the process 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

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. 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

Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Eng, 2016	SR and meta-analysis of RCTs	Inclusion criteria SR: 1) RCTs that compared	Describe intervention: LOCM contrast administration	Describe control: Iodixanol contrast administration	Endpoint of follow-up: 72 hours	Outcome measure-1 Defined as CIN	Facultative: Author's conclusion "No differences were found in CIN risk among

	Literature search up to June 2015 Study design: RCT [parallel] Setting and Country: United States of America Source of funding: non-commercial	LOCM to IOCM with CIn incidence as the main outcome 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	Both ia and iv	Both ia and iv	For how many participants were no complete outcome data available? (intervention/control) Not described	Intra-arterial contrast administration Favours iodixanol: Relative risk (RR): 0.80 (0.64 – 1.01) I^2=43%, p=0.03) Intra-venous contrast administration Favours iodixanol: Relative risk (RR): 0.84 (0.42 – 1.71) I^2=29%, p=0.22)	types of LOCM. Iodixanol 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 osmolar contrast medium; RCT: randomized controlled trial; sCr: serum creatinine.

Evidence table for intervention studies

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 pre-existing status of undergoing long-term Dialysis 3) any record of dialysis within 30 days before or on the day of the CT examination	Describe intervention (treatment/procedure/test): Administration of iso-osmolar contrast medium (IOCM) (iodixanol) prior to Computed Tomography (CT)	Describe control (treatment/procedure/test): Unenhanced 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 iso-osmolar contrast medium and the control groups. The incidence of acute	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 iso-osmolar 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

		N total at baseline: Intervention: 337 Control: 6815 Important prognostic factors[2]: *For example* *age ± SD:* *I: 63 ± 16* *C: 59 ± 19* *Sex:* *I: 65% M* *C: 53% M* Groups comparable at baseline? Yes				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.	(contrast-induced nephrotoxicity) may be overstated and that much of the 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 reported	<u>Inclusion criteria</u>: 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 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>:	Describe intervention (treatment/procedure/test): Contrast-enhanced CT examinations with LOCM	Describe control (treatment/procedure/test): CT examinations without contrast enhancement	<u>Length of follow-up</u>: 72 hours <u>Loss-to-follow-up</u>: 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), 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).	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 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%	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 with a pre-CT eGFR of 45 mL/min/1.73 m^2 or greater."

		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 propensity-matched control <u>N total at baseline</u>: Intervention: 8826 Control: 8826 <u>Important prognostic factors[2]</u>: Age ± SD: I: 59 ± 17 C: 59 ± 18 Sex: I: 48% M C: 48% M Groups comparable at baseline? Yes			<u>Incomplete outcome data</u>: As described above	confidence interval: 1.22, 7.17)	
McDonald, 2014	Type of study: retrospective observational	<u>Inclusion criteria</u>: *1)* all patients who underwent an	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	<u>Length of follow-up</u>: 72 hours	Outcome measures and effect size	Authors' conclusion:

	Setting: in- and outpatients, multicentre study Country: United States of America Source of funding: not reported	unenhanced (non-contrast group) or intravenous contrast-enhanced (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 post-scan SCr results during the time period of expected 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 pre-existing 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	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.	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>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>: As above	(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 non-contrast groups in any risk subgroup after propensity score adjustment by using reported risk factors 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	"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 intravenous iodinated contrast media may not be the causative agent in diminished renal function after contrast material administration."

		N total at baseline: Intervention: 10686 Control: 10686 Important prognostic factors[2]: Age (range): I: Low risk: 62 (49-74) Medium risk: 71 (59-79) High risk: 69 (58-77) C: 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				patient (McNemar test: x2 =0.63, *P* = 0.43) (OR = 0.92; 95% CI: 0.75, 1.13; *P* = .46).	
Hydration versus no hydration at contrast administration							
Chen, 2008	Type of study: RCT Setting: in- and	Inclusion criteria: Patients with myocardial ischemia (angina or positive exercise treadmill) scheduled for	Describe intervention (treatment/procedure/test): sCr<1.5mg/dL:	Describe control (treatment/procedure/test): sCr<1.5mg/dL: No hydration	Length of follow-up: 6 months Loss-to-follow-up:	Outcome measures and effect size (include 95%CI and p-value if available):	Author's conclusion: "Patients with CIN and pre-existing renal

	outpatients, multicentre study Country: China Source of funding: not reported	percutaneous coronary intervention (PCI) in one of the three participating centres. <u>Exclusion criteria</u>: (1) the coronary anatomy not suitable for PCI; (2) emergency coronary artery bypass grafting (CABG) being required; (3) patients in chronic peritoneal or haemodialytic 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]: sCr<1.5mg/dL 85% sCr ≥1.5mg/dL 82%	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 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	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	Not reported <u>Incomplete outcome data</u>: Not reported	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: I: 21.3% C: 34.0% P<0.001	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 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, 2014	Type of study: RCT Setting: in- and outpatients, single centre study Country: Spain Source of funding: not reported	Inclusion criteria: patients who were 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]: Age ± SD: I:62 ± 14 C: 64 ± 12 Sex: I: 72% M C: 75% M Groups comparable at baseline? Yes	Describe intervention (treatment/procedure/test): 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	Describe control (treatment/procedure/test): No hydration Prior to PPCI	Length of follow-up: 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	Outcome measures and effect size (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) haemoglobin before the procedure (OR=0.69 [0.59 to 0.88]; p <0.0001)	Authors' conclusion: "In conclusion, intravenous saline hydration during PPCI reduced the risk of CIN to 48%. Given the higher incidence of CIN in emergency procedures, 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.

					developed heart failure		
Kooiman, 2014	Type of study: RCT Setting: in- and outpatients, single centre Country: the Netherlands Source of funding: non-commercial	<u>Inclusion criteria</u>: 1) Inpatients and outpatients with high clinical suspicion of acute PE requiring CTPA (i.e. Wells score ≥ 4 or 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	Describe intervention (treatment/procedure/test): Sodium bicarbonate hydration prior to CTPA 250 mL intravenous 1.4% sodium bicarbonate 1 h before CTPA without hydration after CTPA.	Describe control (treatment/procedure/test): No hydration prior to CTPA	<u>Length of follow-up</u>: 96 hours for laboratory parameters 2 months for 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	Outcome measures and effect size (include 95%CI and p-value if available): CI-AKI (=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.	Authors' conclusion: "Our results suggest that preventive hydration could be safely withheld in 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."

		Important prognostic factors[2]: Age ± SD: I: 71 ± 13 C: 70 ± 12 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	Inclusion criteria: 1) patients with STEMI who were candidates for primary PCI Exclusion criteria: 1) contrast medium administration within the previous 10 days, 2) end-stage renal failure requiring dialysis, 3) refusal to give informed consent N total at baseline: Intervention: 154 Control: 153 Important prognostic factors[2]: Age ± SD: I:65 ± 13 C: 64 ± 12 Sex:	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.	Length of follow-up: 3 days Loss-to-follow-up: Intervention: 4/150 (3%) 1 had emergency procedure 3 no PCI Control: 3/153 (2%) 1 had emergency procedure 2 no PCI Incomplete outcome data: 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%)	Authors' conclusion: Adequate intravenous volume expansion may prevent CI-AKI in patients undergoing primary PCI. A regimen of preprocedural and postprocedural hydration therapy with sodium bicarbonate appears to be more efficacious than postprocedural hydration only

		I: 77% M C: 73% M Groups comparable at baseline? Unclear				C: 1 (1%) p>0.05	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 Tomography of the pulmonary artery; eGFR: estimated glomerular filtration ration; ia: intra-arterial; IOCM: iso-osmolar contrast medium; iv: intravenous; LOCM: low osmolar 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)

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?	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	
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	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?	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? 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

	Did the study avoid inappropriate exclusions? Yes	Yes	knowledge of the results of the index test? Unclear	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	
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? 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	
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?	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	
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	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	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

	Did the study avoid inappropriate exclusions? Yes	Unclear	knowledge of the results of the index test? 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	
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
	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	

Chen, 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	
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?	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	
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
	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	
Gurm, 2013	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	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

	Did the study avoid inappropriate exclusions? Yes	Unclear	knowledge of the results of the index test? 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	
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 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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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?	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?

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Kul, 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
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Maioli, 2010	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	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

	Did the study avoid inappropriate exclusions? Yes	Unclear	knowledge of the results of the index test? 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	
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 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	
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?	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?

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	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	
Sgura, 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
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Tziakas, 2013	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	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

	Did the study avoid inappropriate exclusions? Yes	Unclear	knowledge of the results of the index test? 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
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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? 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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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?	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?

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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

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 outpatients Country: Turkey Conflicts of interest: not reported	Inclusion criteria: Acute STEMI patients within 12 hours of symptom onset Exclusion criteria: Patients with previous coronary artery bypass N= 402 Prevalence: 32% Mean age ± SD: 63 ± 13 Sex: 76 % M	Describe index test: SYNTAX score Comparator test[2]: Mehran score	Describe reference test[3]: ≥25% increase of serum creatinine concentrations form baseline within 72 hours after PCI	Time between the index test and 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)[4]: Mehran: Sens: 73% 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)	Internal validation only Patients with previous coronary artery bypass were excluded
Bartholomew, 2004	Type of study: cohort Setting: in- and outpatients Country: United States of America	Inclusion criteria: Coronary interventional procedures (single centre) Exclusion criteria: - N= 10 481	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 and 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): External validation Cohort 1: patients admitted for elective PCI N=2689 Discrimination: 0.59 Calibration: NR	

	Conflicts of interest: commercial	Incidence of events: Derivation cohort: 2.8% Validation cohort: 1.2% Mean age ± SD: 65 ± 12 Sex: 67% M			Reasons for incomplete outcome data described? NR	Cohort 2: patients admitted for elective or emergency PCI N=488 Discrimination: 0.58 Calibration: NR	
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 centre Exclusion criteria: - N=1500 Incidence 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 and 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 outpatients Country: China Conflicts of interest: not reported	Inclusion criteria: patients undergoing PCI, single centre Exclusion criteria: - N= 668 Prevalence: 16% Mean age ± SD: 70 ± 6 Sex: 48% M	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 and 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): External validation Elderly patients at same 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 centre Exclusion criteria: - N=2764 Incidence of events: Derivation cohort: 5.5% Validation cohort: 5.0%	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 and 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

		Mean age ± SD: 60 ± 11 Sex: 71% M					
Ghani, 2009	Type of study[7]: cohort study Setting: in- and outpatients Country: Kuwait Conflicts of interest: not reported	Inclusion criteria: patients undergoing PCI, single centre Exclusion criteria: - N= 247 Incidence of events: Derivation cohort: 5.5% Validation cohort: 5.0% Mean age ± SD: 63 ± 10 Sex: 68% M	Describe index test: "Simple risk score for CIN"	Describe reference test: >0.5 mg/dL increase in serum creatinine within 48 hours of PCI	Time between the index test and 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: <4: 9.2% 5-8: 32% 9-12: 54% >12: 84%	Internal validation only
Gurm, 2014	Type of study[8]: cohort study Setting: in- and outpatients	Inclusion criteria: patients undergoing PCI, multiple centre Exclusion criteria:	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 and reference test: 7 days For how many participants were no complete outcome data available?	Outcome measures and effect size (include 95%CI and p-value if available): AUC: 0.88 Risk score range associated with PC-AKI:	Internal validation only

	Country: United States of America / the Netherlands Conflicts of interest: not reported	1) patients on dialysis 2) patients with missing serum creatinine values N= 48001 Prevalence: 3% Mean age ± SD: 65 ± 12 Sex: NR			NR Reasons for incomplete outcome data described? NR	Low: 0.5% Medium: 2.8% High: 13% Incidence of events: Derivation cohort: 2.6% 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 coronary 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 and 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	Inclusion criteria: PCI, single centre	Describe index test: Mehran risk score	Describe reference test: ≥25% or 44.2µmol/L increase in serum	Time between the index test and reference test: 48 hours	Outcome measures and effect size (include 95%CI and p-value if available): AUC: 0.59	Internal validation only

	Setting: in- and outpatients Country: France Conflicts of interest: not reported	Exclusion criteria: - N=322 Prevalence:9% Mean age ± SD: 64 ± 14 Sex: 66% M		creatinine following contrast administration	For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	CIN incidence: 9%	
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 and 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	Inclusion criteria: patients with acute STEMI and	Describe index test: Zwolle risk score	Describe reference test: >0.5 mg/dL or 25% increase in serum	Time between the index test and reference test: 72 hours	Outcome measures and effect size (include 95%CI and p-value if available): 1) Zwolle score >2	Internal validation only

	Setting: in- and outpatients Country: Turkey Conflicts of interest: not reported	undergoing emergency PCI Exclusion criteria: - N= 314 Prevalence: 12% Mean age ± SD: 56 ± 11 Sex: 81% M	Comparator test: Mehran risk score	creatinine within 72 hours of PCI	For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Sens: 76% Spec: 75% AUC: 0.85 2) Mehran score > 5 Sens: 71% 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 centre (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 and 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 Country: Italy Conflicts of interest: not reported	Inclusion criteria: patients with an indication for coronary angiography or PCI, single centre Exclusion criteria: - N=1281 Prevalence: 3% Mean age ± SD: 69 ± 10 Sex: 67% M	Describe index test: Global Registry for Acute Coronary Events (GRACE) risk score Comparator test: Mehran risk score	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 and 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): GRACE Cut-off 160 Sens: 79% 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	Risk score range associated with PC-AKI risk: 0-1: 0% 2-3: 1% 4: 2% 5: 6% 6: 12% 7: 19% 8: 24% 9: 36% 10: 50%
Marenzi, 2004	Type of study[15]: cohort study Setting: in- and outpatients	Inclusion criteria: patients referred for PCI for STEMI, single centre Exclusion criteria:	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 and reference test: 5 days For how many participants were no complete outcome data available?	Outcome measures and effect size (include 95%CI and p-value if available): External validation N=891 Discrimination 0.57 and calibration NR	

	Country: Italy Conflicts of interest: not reported	N= 218 Incidence of events: Derivation cohort: 19% Validation cohort: 14% M			NR Reasons for incomplete outcome data described? NR		
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 centre 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 and 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 centre N=3945 Discrimination: 0.57 Calibration: NR Cohort 2: patients admitted for elective or emergency PCI, single centre	

						N=5571 Discrimination: 0.59 Calibration: NR	
Mizuno, 2014	Type of study[17]: cohort study Setting: in- and outpatients Country: Japan Conflicts of interest: not reported	Inclusion criteria: patients undergoing a PCI for STEMI, single centre Exclusion criteria: - N= 102 Prevalence: 10% Mean age ± SD: 62 ± 14 Sex: 78 % M	Describe index test: Mehran Risk score (and red cell distribution width)	Describe reference test: >0.5 mg/dL or 25% increase in serum creatinine within 3 days of PCI	Time between the index test and reference test: 3 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 Mehran: 0.72 (0.54 – 0.90)	Internal validation only
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 coronary angiography Exclusion criteria: - N=202 Prevalence: 28%	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 and 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

		Mean age ± SD: 63 ± 13 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 centre 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 and 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	Inclusion criteria: Elective or emergency PCI, single center Exclusion criteria: - N= 688	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 and 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): Calibration / discrimination: 0.76 p>0.05 External validation	

	Conflicts of interest: not reported	Incidence of events: Derivation cohort: 10% Validation cohort: 14% Mean age ± SD: 64 ± 11 Sex: 74% M			Reasons for incomplete outcome data described? NR	Cohort 1: PCI patient same single centre N=200 Discrimination: 0.86 Calibration: NR Cohort 2: patients admitted for elective or emergency PCI, multiple centres (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 centres 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 and 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	Inclusion criteria: patients with an	Describe index test:	Describe reference test:	Time between the index test and reference test: 48 hours	Outcome measures and effect size (include 95%CI and p-value if available):	

)

	Setting: in- and outpatients Country: India Conflicts of interest: not reported	indication for PCI, single centre Exclusion criteria: - N=900 Incidence of events: Derivation cohort: 9.7% Validation cohort: 8.7% Mean age ± SD: 57 v 10 Sex: 84% M	"Simple risk score for CIN"	>0.5 mg/dL or 25% increase in serum creatinine within 48 hours of PCI	For how many participants were no complete outcome data available? NR Reasons for incomplete outcome data described? NR	Sens: 94% 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	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)	311

English, Dutch	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) 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)	

2.3 Evaluation of eGFR

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.

2.4 Prevention of PC-AKI

2.4.1 Hydration and complications

Table of excluded studies

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 fulfil 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 fulfil inclusion criteria (compares iv hydration with N-acetylcysteine 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 fulfil 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 tables

Quality assessment table

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 described: "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 described: "randomly assigned"	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unlikely
Huber, 2016	Computer-generated randomization list	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Manari, 2014	Computer generated balanced randomization list	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Ozcan, 2007	Not described: "randomly assigned"	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear

Ratcliffe, 2009	Not described: "randomization block"	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Likely	Unclear
Recio-Mayoral, 2007	Not described: "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 centre	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	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear

	(random numbers table)							
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 a web-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 randomisation schedule	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely
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

Evidence table for intervention studies

Study reference	Study characteristics	Patient characteristics 2	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Hydration versus no hydration							
Kooiman, 2014	Type of study: randomized	Inclusion criteria:	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	Length of follow-up:	Outcome measures and effect size	Authors' conclusion:

	controlled trial Setting: emergency patients, multiple centers, both in- and outpatients Country: the Netherlands Source of funding: non-commercial	1) adult patients ≥18 years with a clinical suspicion of a pulmonary embolism requiring computed tomography-pulmonary angiography (CTPA) 2) chronic kidney disease (CKD): eGFR <60mL/min/1.73m2 Exclusion criteria: 1) pregnancy 2) previous contrast administration within past 7 days 3) documented allergy for iodinated contrast media 4) hemodynamic instability (systolic blood pressure <100mmHg) 5) earlier participation in same trial N total at baseline: Intervention: 67 Control: 71 Important prognostic factors2: For example	Withholding hydration prior to CTPA	250mL iv 1.4% sodium bicarbonate 1 hour before CTPA	96 hours Loss-to-follow-up: 3/138 (2.2%) 2 lost to follow-up 1 died Incomplete outcome data: As above	(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	"Our results suggest that preventive hydration could be safely withheld in CKD patients undergoing CTPA for suspected acute pulmonary embolism."

		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 patients, one university hospital Country: the Netherlands Source of funding: Stichting de Weijerhorst	Inclusion criteria: 1) eGFR: 45-59 mL/min/1.73m2 combined with either diabetes, or at least two 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).	Describe intervention (treatment/procedure/test): Prophylactic hydration protocols according to current guidelines: 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.	Describe control (treatment/procedure/test): No prophylactic treatment.	Length of follow-up: 2-6 days Loss-to-follow-up: I: 68/328 C: 25/332 Incomplete outcome data: As above	Outcome measures and effect size (include 95%CI and p-value if available): 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	Authors' conclusion: "We found no prophylaxis to be non-inferior and cost-saving in preventing contrast-induced nephropathy compared with intravenous hydration according to current clinical practice guidelines."

		Exclusion criteria: 1) Inability to obtain informed consent; 2) eGFR lower than 30mL per min/1.73m2; 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 other RCT; and 9) isolation due to infection control N total at baseline: Intervention: 328 (I1: 328, I2: 296) Control: 332 (C1: 332, C2: 307) Important prognostic factors2: For example age ± SD: I: 71.9 ± 9.3				35 days.	

		C: 72.6 ± 9.3 Sex: I: 59% M C: 64% M Baseline SCr: I:118.7±28µmol/L C:117.7±25µmol/L Groups comparable at baseline? Yes					
Oral hydration							
Cho, 2010	Type of study: randomized controlled trial Setting: elective patients, one hospital Country: United States of America Source of funding: not reported	Inclusion criteria: 1) patients 18 years or older with stable serum creatinine levels of at least 1.1mg/dL or estimated creatinine clearance less than 60mL/min scheduled for diagnostic, elective angiography Exclusion criteria: 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	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 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	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 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	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 (= >25% increase in sCr from baseline 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	Authors' hydration: "Oral hydration with or without sodium bicarbonate prior to and following CAG is not inferior 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 function after contrast exposure without occurring additional delay in hospital days or in-hospital mortality."

		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 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				There were no in-hospital mortalities during this study. Length of hospital stay did not differ significantly between groups.	

		than 28eEw/L and sodium less than 133mEq/L N total at baseline: Intervention: 43 (I1: 22, I2: 22) Control: 48 (C1: 27, C2: 21) Important prognostic factors[2]: 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	Inclusion criteria: 1) patients referred for any radiological procedures necessitating a	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	Length of follow-up: 48 hours	Outcome measures and effect size (include 95%CI and p-value if available):	Authors' conclusion: "Oral saline hydration was as efficient as

	Setting: elective patients, one university hospital Country: France Source of funding: non-commercial	contrast medium injection and who had a baseline Cockcroft clearance between 15-60ml/min 2) either chronic renal failure and on a kidney graft Exclusion criteria: 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 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			Loss-to-follow-up: Not reported per group separately, in total 3/315 (1%) lost to follow-up Incomplete outcome data: As above	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	intravenous saline hydration for the prevention of CIN in patients with stage 3 renal diseases."

		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 N total at baseline: Intervention: Control: Important prognostic factors2: 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	Inclusion criteria: 1) patients >18 years with baseline serum creatinine concentration greater than 106µmol/L (1.2mg/dL) undergoing elective diagnostic or interventional coronary angiography Exclusion criteria: 1) acute myocardial infarction 2) allergies to trial medication 3) exposure to contrast medium within 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,	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	Length of follow-up: 2 days Loss-to-follow-up: 1 patient (refused follow-up) Incomplete outcome data: 3/145 (2%) 2 patients had an emergency coronary bypass and pulmonary oedema 1 patient refused follow-up	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 not required	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."

		fenoldopam or NAC during the study N total at baseline: Intervention: 71 Control: 74 Important prognostic factors2: 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 Groups comparable at baseline? Yes					
Boucek, 2013	Type of study: RCT Setting: elective inpatients, one hospital Country: Czech Republic	Inclusion criteria: 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	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)	Length of follow-up: 2 days – laboratory parameters 1 month – clinical parameters Loss-to-follow-up: Intervention: 3/61 (5%)	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 following	Authors' conclusion: "In diabetic patients with renal function impairment sodium bicarbonate does not confer protection against contrast-induced nephropathy greater than

	Source of funding: commercial	intravenous use of contrast Exclusion criteria: 1) end-stage 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 (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			Reasons not described Control: 3/59 (5%) Reasons not described Incomplete outcome data: As above	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.	sodium chloride-based hydration.”

		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 N total at baseline: Intervention: 61 Control: 59 Important prognostic factors[2]: Age ± SD: I: 63 ± 11 C: 67 ± 10 Sex: I: 75% M C: 75% M eGFR (mL/min/1.73m2) ± 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 following: -diabetes mellitus, -history of congestive heart failure, -hypertension (140/90 mm Hg treatment with an antihypertensive medication), -age older than 75 years Exclusion criteria: 1) inability to obtain consent, 2) receipt of a sodium bicarbonate infusion prior to randomization, 3) emergency cardiac catheterization, 4) intra-aortic balloon counter pulsation,	Describe intervention (treatment/procedure/test): 1.4% sodium bicarbonate iv infusion. Infusion was begun 1 hour prior to the start of contrast administration at 3 mL/kg for1hour, decreased to 1.5 mL/kg per hour during the procedure and for 4 hours following completion of the procedure. For patients weighing more than 100 kg, the bolus and infusion rate were limited to those used for patients weighing 100kg/	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 the procedure. For patients weighing more than 100 kg, the bolus and infusion rate were limited to those used for patients weighing 100kg.	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 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	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 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	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 severe chronic kidney disease who are undergoing coronary angiography."

		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 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 N total at baseline: Intervention: 175 Control: 178			estimated GFR data 1-4 d after procedure Incomplete outcome data: As above for laboratory parameters. All patients were followed up for clinical events.	6-month start of dialysis I: 2/175 (1%) C: 4/178 (2%) P-value not reported	

		Important prognostic factors2: 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 difference centres Country: Brazil Source of funding: none reported	Inclusion criteria: 1) patients at moderate to high risk for developing CIN who were referred for elective coronary angiography or PCI at 6 centres 2) serum creatinine ≥ 1.2 mg/dL or glomerular filtration rate (GFR) <50 mL/min Exclusion criteria: 1) age <18 years, 2) use of radiographic contrast media during the last 21 days, 3) history of dialysis,	Describe intervention (treatment/procedure/test): 154 mEq/l of sodium bicarbonate in 5% dextrose and H2O 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	Describe control (treatment/procedure/test): 0.9% saline infusion 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	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 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%	Authors' conclusion: "Hydration with sodium bicarbonate was not superior to saline to prevent contrast media induced nephropathy in patients at risk undergoing cardiac catheterization."

		4) cardiac insufficiency class III-IV NYHA, 5) emergency procedures N total at baseline: Intervention: 150 Control: 151 Important prognostic factors[2]: Age ± SD: I: 64 ± 12 C: 65 ± 12 Sex: I: 69% M C: 75% M eGFR ± SD I: 51 ± 13 C: 52 ± 13 Groups comparable at baseline? Yes				P=0.81	
Huber, 2016	Type of study: randomized controlled trial Setting: single-centre university hospital	Inclusion criteria: 1) >18 years; 2) increased risk of CIN undergoing administration of CM. High risk was defined by a serum creatinine level ≥1.1 or ≥0.8 mg/dL plus an	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.	Length of follow-up: 48h after CM Loss-to-follow-up: I:14/91 C: 14/94 Incomplete outcome data:	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	Authors' conclusion: "In patients at increased risk of CIN receiving prophylactic theophylline, hydration with sodium bicarbonate

	Country: Germany Source of funding: institutional support	additional risk factor like diabetes mellitus, renal failure in past medical history, or nephrotoxic medication (aminoglycoside, vancomycin, amphotericin B, and diuretic). Exclusion criteria: 1) pre-existing renal replacement therapy; 2) unstable serum creatinine levels (difference of more than _0.4 mg/dL within 3 days before contrast application); 3) contra-indications for theophylline or sodium bicarbonate (allergies, tachycardia, alkalosis, and hypokalaemia); and; 4) additional interventions that might			Not reported	after contrast application I: 1/74 (1.4%) C: 7/78 (9%) P=0.039 Dialysis: I: 9% C: 17% P=0.189	reduces contrast-induced renal impairment compared to hydration with saline.”

		influence renal function. Important prognostic factors2: 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 trial 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 ST segment elevation of 0.2mV or more in at least two	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	Authors' conclusion "In patients with STEMI undergoing PPCI, high volume hydration with normal saline or sodium bicarbonate administrated at the time of contrast media administration was not associated with any significant advantage in terms

		contiguous leads or new left bundle-branch block Exclusion criteria: 1) the concomitant detection of mechanical complications, 2) previous peritoneal or haemodialysis treatment, 3) the presence of post anoxic coma 4) pregnancy N total at baseline: Intervention 1: 145 Intervention 2: 154 Control 1: 142 Control 2: 151 Important prognostic factors[2]: 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				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).	of CI-AKI prevention.”

		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 funding: not reported	Inclusion criteria: patients who were scheduled for coronary angiography or percutaneous coronary intervention and had a baseline creatinine level N1.2 mg/dL 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	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	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 in serum creatinine N25% or 0.5 mg/dL after 48 hours) I: 12/88 C: 4/88 P=0.043 RR (adjusted): 0.29 95% CI: 0.09 – 0.96	Authors' conclusion "Hydration with sodium bicarbonate provides better protection against CIN than the sodium chloride infusion does alone."

		N total at baseline: Intervention: 88 Control: 88 Important prognostic factors[2]: Age median (minimum – maximum) I: 68 (43-86) C: 70 (40-84) Sex: I: 73% M C: 75% M Creatinine clearance (mL/min) I: 53 (21 – 81) C: 50 (22-101) Groups comparable at baseline? Yes					
Ratcliffe, 2009	Type of study: randomized controlled trial Setting: elective patients, single centre Country: United States of America	Inclusion criteria: 1) ambulatory or hospitalized patients who were scheduled for invasive coronary angiography or percutaneous coronary intervention for the evaluation and treatment of	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	Length of follow-up: 72 hours Loss-to-follow-up: Intervention: 15/30 (50%) Reasons: 11 lack of complete follow-up	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	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

	Source of funding: not reported	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 in women) or reduced calculated creatinine clearance (less than 1.002 mL/s) using the Cockcroft-Gault formula, and/or diabetes mellitus on oral antiglycaemic or insulin therapy Exclusion criteria: 1) pregnancy or lactation; 2) acute myocardial infarction;			4 other reasons Control: 10/29 (30%) 8 lack of complete follow-up 2 other reasons Incomplete outcome data: As above	administration of the contrast media) I: 2/19 (11%) C: 1/15 (7%) p>0.05	NAC did not have an effect on the incidence of CIN."

		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 N total at baseline: Intervention: Control:					

		Important prognostic factors[2]: 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 Country: United Kingdom Source of funding: not reported	Inclusion criteria: 1) acute coronary syndrome (ACS) patients who were admitted to our coronary care unit 2) patients with myocardial infarction treated with primary PCI or rescue PCI, as well as patients with high-risk non–ST-segment elevation ACS needing urgent revascularization Exclusion criteria: 1) end-stage renal failure on dialysis, 2) uncontrolled hypertension (systolic blood pressure	Describe intervention (treatment/procedure/test): Active prophylactic treatment of PCI: Intravenous bolus of 5 ml/kg/h of alkaline saline solution with 154 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.	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 orally the next day	Length of follow-up: 3 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 =an absolute 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	Authors' conclusion: "Rapid intravenous hydration with sodium bicarbonate plus N-AC before contrast injection is effective and safe in the prevention of CIN in patients undergoing emergency PCI."

		>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 N total at baseline: Intervention: 56 Control: 55 Important prognostic factors[2]: 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	Inclusion criteria: 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 m2 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,	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).	Length of follow-up: 48 hours for laboratory parameters 5 days for clnical events Loss-to-follow-up: Intervention: 9/117 (8%) 8 had no follow-up sCr value 1 had no contrast exposure Control: 7/118(6%) 7 had no follow-up sCr value Incomplete outcome data: As above	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%) p-value not reported	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."

		7) administration of theophylline, dopamine, mannitol, or fenoldopam N total at baseline: Intervention: 111 Control: 108 Important prognostic factors[2]: Age ± SD: I: 70 ± 9 C: 71 ± 9 Sex: I: 88% M C: 81% M Groups comparable at baseline? Yes					
Castini, 2008	Type of study: randomized controlled trial Setting: one hospital Country: Italy Source of funding: not reported	Inclusion criteria: 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 Exclusion criteria:	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	Length of follow-up: 5 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): CIN1 (=an increase in serum creatinine concentration≥25% over the baseline value in any of the 3 predefined time-points: 24 hours,	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

		1) serum creatinine levels >4 mg/dL, 2) a history of dialysis, 3) multiple myeloma, 4) pulmonary oedema, 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, 10) previous enrolment in the same or other protocols, 11) pregnancy, 12) administration of theophylline, mannitol, dopamine, dobutamine, nonsteroidal anti-inflammatory drugs, or fenoldopam. N total at baseline:				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.	with isotonic saline infusion.”

		Intervention: 52 Control: 51 Important prognostic factors[2]: 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: elective patients, two tertiary hospitals Country: United states of America Source of funding: not reported	Inclusion criteria: 1) patients undergoing elective coronary and peripheral 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	Describe intervention (treatment/procedure/test): Dextrose 5% in water containing 154 mEq/L of NaHCO3 with or 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	Describe control (treatment/procedure/test): Intravenous 0.9% normal saline with or 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	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): 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	Authors' conclusion: "Incidence of CI-AKI was no different in the NaHCO3 group compared to saline group, and NAC did not reduce CI-AKI in the two study arms."

		Exclusion criteria: (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 oedema, (4) had serum bicarbonate level >34 mmol/L; (5) received fenoldapam, mannitol, dopamine, or NAC within 48 hr prior to 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				patient population during the study period.	

		Important prognostic factors[2]: 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: elective patients, multi-centre trial Country: Switzerland Source of funding: commercial and non-commercial	Inclusion criteria: All patients admitted with renal dysfunction {actual serum creatinine 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	Describe intervention (treatment/procedure/test): The initial intravenous bolus was 3 mL/kg/h of 166 mEq/L sodium 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.	Describe control (treatment/procedure/test): The infusion of 0.9% sodium chloride was administered at a 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.	Length of follow-up: 48 hours Loss-to-follow-up: Intervention: 6/93 (6%) 5 received no radiocontrast 1 refused participation Control: 4/93 (4%) 4 received no radiocontrast	Outcome measures and effect size (include 95%CI and p-value if available): 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	Authors' conclusion: "Volume supplementation with 24 h sodium chloride 0.9% is superior to sodium bicarbonate for the prevention of CIN."

		Diet in Renal Disease (MDRD) study equation16]} scheduled to undergo an intra-arterial or intravenous radiographic contrast procedure on the next day Exclusion criteria: 1) age ≥18 years, 2) pre-existing dialysis, allergy to radiographic contrast, 3) pregnancy, 4) severe heart failure (NYHA functional class III and IV), 5) N-acetylcysteine ≤24 h before contrast, 6) clinical condition requiring continuous fluid therapy, e.g. severe sepsis N total at baseline: Intervention: 87 Control: 89			Incomplete outcome data: As above	event related to the infusion (death, intensive care unit admission). Also, no patient required intravenous diuretics or nitrates due to pulmonary congestion.	

		Important prognostic factors[2]: 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 patients, multicentre trial academic hospitals Country: Korea Source of funding: not reported	Inclusion criteria: 1) patients undergoing coronary or endovascular angiography or intervention 2) serum creatinine ≥1.1 mg/dl, estimated glomerular filtration rate (eGFR) ≤60 ml/min/1.73 m2, 3) age ≥18 years, 4) diagnosis with diabetes mellitus Exclusion criteria:	Describe intervention (treatment/procedure/test): Sodium bicarbonate infusion (154 mEq/L in dextrose and water) was 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	Describe control (treatment/procedure/test): 0.9% sodium chloride 1 ml/kg/hour for 12 hours before and after the procedure All patients received NAC 1,200 mg 2 times/day for 2 days starting the day before the index procedure	Length of follow-up: 48 hours for laboratory parameters 6 months for clinical parameters Loss-to-follow-up: Intervention: 5/193 (3%) All had no laboratory data Control: 2/189 (1%)	Outcome measures and effect size (include 95%CI and p-value if available): 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	Authors' conclusion: "In conclusion, hydration with sodium bicarbonate is not superior to hydration with sodium chloride in preventing CIN in patients with diabetic nephropathy undergoing coronary or endovascular angiography or intervention."

		1) inability to obtain informed consent, 2) serum creatinine ≥8 mg/dl, eGFR ≤15 ml/min/1.73 m2 at rest, end-stage renal disease on haemodialysis, 3) multiple myeloma, 4) pulmonary oedema, 5) uncontrolled hypertension (systolic pressure >160 mm Hg or diastolic pressure >100 mm Hg), 6) acute ST-segment elevation myocardial infarction while 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			All had no laboratory data Incomplete outcome data: As above	Requirement of haemodialysis 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.	Infusion rates were decreased to 0.5 ml/kg/hour in patients with left ventricular ejection fraction ≤45% in the 2 treatment arms.

		11) medications such as theophylline, dopamine, mannitol, fenoldopam, and NAC N total at baseline: Intervention: 193 Control: 189 Important prognostic factors[2]: 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 centre	Inclusion criteria: 1) patients with pre-angiographic estimated creatinine clearance <60 ml/min 2) undergoing planned	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.	Describe control (treatment/procedure/test): 1 ml/kg/h 0.9% sodium chloride for 12 h before and after the procedure	Length of follow-up: 5 days Loss-to-follow-up: Intervention: 4/252 (2%) 3 died	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	Authors' conclusion: "Hydration with sodium bicarbonate plus NAC before contrast medium exposure is not more effective

	Country: Italy Source of funding: not reported	angiographic procedures Exclusion criteria: 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 N total at baseline: Intervention: 250 Control: 252 Important prognostic factors[2]: Age median (IQR): 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	All patients received 600 mg oral NAC twice a day from the day before to the day after the procedure		1 acute renal failure Control: 5/250 (2%) 4 died 1 acute renal failure Incomplete outcome data: As above	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 Death and acute renal failure, see column “Follow-up” for numbers, no significant difference in clinical events.	than hydration with isotonic saline plus NAC for prophylaxis of CIN in patients with moderate-to-severe renal dysfunction.”

Nieto-Rios, 2014	Type of study: randomized controlled trial Setting: elective patients, single centre Country: Colombia Source of funding: not reported	Inclusion criteria: 1) Inpatients in a tertiary centre, 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, Exclusion criteria: 1) current clinical diagnosis of exacerbated congestive heart failure, 2) ejection fraction <35% by previous echocardiography, 3) signs of acute pulmonary oedema within 48 hours before the procedure, 4) systolic blood pressure <90 mmHg or requirement of vasopressors support,	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	Length of follow-up: 5 days Loss-to-follow-up: Intervention: 7/107 (7%) 3 died 1 withdrawal 3 technical difficulties Control: 1/113 (1%) 1 died Incomplete outcome data: 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%) P=0.34	Authors conclusion: “Our investigation showed that there were no differences between normal saline solution (extended infusion) vs. bicarbonate solution for nephroprotection.”

		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 hypokalaemia induced by bicarbonate), 12) uncompensated diabetes mellitus (four different values >200 mg/dL in the previous 24 hours) 13) patient or physician refusal to participate. N total at baseline: Intervention: 107					

		Control: 113 Important prognostic factors[2]: 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 patients, single-centre Country: Israel Source of funding: not reported	Inclusion criteria: 1) patients with chronic kidney disease (CKD) stage III–IV undergoing cardiac catheterization Exclusion criteria: 1) plasma creatinine levels more than 8 mg/dL or eGFR less than 15 mL/min, change in plasma creatinine levels of ≥0.5	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 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	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 catheterization and NAC 600 mg × 2/d orally the day before and the day of the procedure	Length of follow-up: 2 days Loss-to-follow-up: Intervention: 0 (0%) Control: 5/41 (12%) No laboratory evaluation at baseline or after contrast exposure	Outcome measures and effect size (include 95%CI and p-value if available): 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	Authors' conclusion: "Hydration with sodium bicarbonate is not 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."

		mg/dL during the previous 24 hours, 2) pre-existing dialysis, multiple myeloma, 3) pulmonary oedema, 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 N total at baseline: Intervention: 51 Control: 36 Important prognostic factors[2]: Age ± SD: I: 72 ± 10 C: 71 ± 9 Sex: I: 84% M C: 70% M	drip were limited to those doses administered to patients weighing 110 kg.		Incomplete outcome data: As above	(=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.	

		eGFR (ml/min/1.73m2) ± 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 cardiac catheterisation with or without PCI 4) were able to receive Prehydration for 12 h. Exclusion criteria: 1) end-stage renal failure with GFR of	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)	Length of follow-up: 48 hrs Loss-to-follow-up: 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 catheterisation or PCI I1: 6.5% I2: 12.8% C1: 10.6% P=0.214	Authors' conclusion "The combination regimen was not superior to individual regimens in preventing CIN in patients with baseline renal impairment. There was a trend suggesting that the 12-hour sustained sodium chloride Prehydration regimen was more protective than the 1-hour abbreviated SOB regimen."

		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 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; Important prognostic factors[2]: 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	Inclusion criteria: 1) patients undergoing coronary angiography or intervention 2) ≥20 years old 3) had an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m2 Exclusion criteria: 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 oedema, 5) uncontrolled hypertension (treated systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg), 6) emergency catheterization, 7) exposure to radiographic	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.	Length of follow-up: 1 months Loss-to-follow-up: Intervention: 2/79 (2%) No laboratory test results Control: 1/79 (1%) Analgia due to sodium bicarbonate infusion Incomplete outcome data: 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 haemodialysis.	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."

		contrast within previous 2 days, 8) any allergy to radiographic contrast medium N total at baseline: Intervention: 77 Control: 78 Important prognostic factors2: 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 Setting: elective patients, two hospitals Country: Japan	Inclusion criteria: 1) Patients who were scheduled for elective coronary arteriography or percutaneous coronary intervention 2) age >20 years 3) serum creatinine (Cr) level >1.1 to <2.0 mg/dl.	Describe intervention (treatment/procedure/test): Standard hydration with sodium 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	Describe control (treatment/procedure/test): Standard hydration with sodium 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.	Length of follow-up: 3 days Loss-to-follow-up: All patients completed the study Incomplete outcome data:	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=an increase ≥25% or ≥0.5 mg/dl in serum Cr within the first 3 days after the procedure	Authors' conclusion "In conclusion, single-bolus intravenous administration of sodium bicarbonate in addition to standard hydration can more effectively prevent CIN than standard

	Source of funding: not reported	Exclusion criteria: 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 N-acetylcysteine, theophylline, dopamine, or mannitol N total at baseline: Intervention: 72 Control: 72		For patients weighing >80 kg, infusion rate was limited to 80 ml/hour (40 ml/hour for patients with left ventricular ejection fraction _40%).	All patients completed the study	compared to baseline value) I: 1.4% C: 12.5% P=0.017 Adverse clinical events (acute pulmonary oedema, acute renal failure requiring dialysis, and death within 7 days of procedure) I: 0% C: 1.4% p>0.05	hydration alone in patients with mild renal insufficiency undergoing an elective coronary procedure.”

		Important prognostic factors[2]: 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 centre Country: Turkey Source of funding: not reported	Inclusion criteria: 1) Undergoing contrast-enhanced thoracic CT due to suspected PE; 2) aged over 18 years; 3) with measure-able basal creatinine levels pre-tomography and; 4) measurable serum creatinine levels 48– 72 hours post-tomography, and with one or more of the risk factors for CIN. The risk factors were pre-existing renal dysfunction (Cr 1.4 mg/dL or a high or calculated	Describe intervention (treatment/procedure/test): I1: 3 mL/kg intravenous 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 intravenous per hour for a minimum of 6 hour after CTPA.	Length of follow-up: 48-72 hrs Loss-to-follow-up: 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 ≥25% or 0.5 mg/dL I1: 23.5% I2: 21.2% C1: 26.4% P=0.719	Authors' conclusion "In conclusion, there were no statistically significant differences observed among prophylactic NAC, NaHCO3, and NS in prevention of CIN following contrast-enhanced CTPA."

		glomerular filtration rate [GFR] < 60 mL/min/1.73 m2), 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 anaemia (haematocrit < 30%). Exclusion criteria: 1) end-stage renal disease already in peritoneal dialysis; 2) haemodialysis; 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 Important prognostic factors[2]: 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	Inclusion criteria:	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	Length of follow-up:	Outcome measures and effect size	Authors' conclusion

	controlled trial Setting: emergency patients, single centre Country: Japan Source of funding: not reported	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 glomerular filtration rate (eGFR) of <60 ml/min Exclusion criteria: 1) change in the serum Cr concentration of >0.5 mg/dl during the 24 hours before the procedure, 2) pre-existing dialysis, exposure to the contrast	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	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	2 days Loss-to-follow-up: Intervention: 0 (0%) Control: 1/30 (3%) Circulatory failure Incomplete outcome data: As above	(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 developed acute renal failure requiring haemodialysis.	"In conclusion, rapid alkalization by bolus injection of sodium bicarbonate was effective for the prevention of CIN in patients with CKD undergoing emergent procedures."

		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 non-study sodium bicarbonate N total at baseline: Intervention: 30 Control: 29 Important prognostic factors[2]: Age ± SD: I: 77 ± 9 C: 75 ± 10 Sex: I: 79% M C: 77% M 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, multicentre trial Country: the Netherlands Source of funding: non-commercial	Inclusion criteria: 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 m2 estimated by the Modification of Diet in Renal Disease formula 3) eligible for the fluid challenge of saline hydration Exclusion criteria: 1) pregnancy, 2) previous contrast administration within the last 7 days, 3) documented allergy for iodinated contrast media, 4) haemodynamic instability (systolic blood pressure <100 mmHg) 5) previous participation in the trial	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	Length of follow-up: 96 hours Loss-to-follow-up: 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 Incomplete outcome data: As above	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 versus 6 of 281 patients in the saline group (P = 0.03) None of the CI-AKI patients developed	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."

		N total at baseline: Intervention: 267 Control: 281 Important prognostic factors[2]: 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				a need for dialysis.	
Controlled diuresis for coronary angiography and/or percutaneous intervention							
Barbanti, 2016	Type of study: randomized controlled trial Setting: university hospital Country: Italy Source of funding: not reported	Inclusion criteria: 1) All patients with symptomatic severe aortic stenosis undergoing TAVI were considered eligible Exclusion criteria: 1) chronic end-stage renal failure on dialysis; 2) episode of acute congestive heart failure with left	Describe intervention (treatment/procedure/test): Renal Guard therapy received hydration with a normal saline solution; with an initial bolus (priming) of 250 ml was infused over 30 min (preprocedural. Urine flow was monitored and maintained at the target value throughout the procedure and during the following 4 h. phase).	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 procedure.	Length of follow-up: 78 hrs Loss-to-follow-up: No loss to follow-up	Outcome measures and effect size (include 95%CI and p-value if available): AKI (defined: absolute 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	Authors' conclusion "In summary, furosemide-induced diuresis with matched isotonic intravenous hydration using the Renal Guard system is an effective therapeutic tool to reduce the occurrence of AKI

		ventricular ejection fraction <30% in the past 30 days before randomization; 3) contraindications to placement of a Foley catheter; 4) urgent TAVI 5) unavailability of the Renal Guard system. Important prognostic factors[2]: 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				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 death I: 0/56(0%) C: 1/56 (1.8%) P=0.306	in patients undergoing TAVR.”

						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 centre Country: United states of America Source of funding: not reported	Inclusion criteria: 1) patients referred to the cardiac catheterisation laboratory 2) an estimated glomerular filtration rate (GFR) of 60 mL/min per 1・73 m2 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 obtain consent from participants, 2) emergency cardiac catheterisation (eg,	Describe intervention (treatment/procedure/test): 0.9% sodium chloride bolus infusion at 3 mL/kg for 1 h The fluid 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 fluid 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 fluid 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: 28/200 (14%) 24 had 1 sCr value	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 In total, six patients (1・5%)—three in each group—	Authors' conclusion: "Left ventricular end-diastolic pressure-guided fluid administration seems to be safe and effective in preventing contrast-induced acute kidney injury in patients undergoing cardiac catheterisation."

		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 7.5% or more per day or a cumulative change of 15% or more during the			4 had no sCr value	terminated the intravenous fluids early, the reason for which was shortness of breath in all six patients.	

		preceding 2 or more days. N total at baseline: Intervention: 196 Control: 200 Important prognostic factors[2]: 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, multicentre Country: Italy	Inclusion criteria: 1) patients with chronic kidney disease scheduled for coronary and/or peripheral angiography and/or angioplasty with an estimated glomerular filtration rate (eGFR) ≤30mL /min/ 1.73 m2	Describe intervention (treatment/procedure/test): Hydration with normal saline plus NAC controlled by the Renal Guard system NAC was administered only iv (1500 mg in 1L saline) during the 3 phases (preprocedural, intraprocedural, and postprocedural) of the Renal Guard therapy.	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 a rate of 1 mL/kg per hour during contrast exposure and for 6 hours after the procedure.	Length of follow-up: 1 week Loss-to-follow-up: 0 (0%) in both groups Incomplete outcome data: Intervention: 0 (0%)	Outcome measures and effect size (include 95%CI and p-value if available): CI-AKI (=an increase in sCr concentration ≥0.3 mg/dL above the baseline value at 48 hours after administration of Contrast or the	Authors' conclusion: "Renal Guard therapy is superior to sodium bicarbonate and N-acetylcysteine in preventing contrast-induced acute kidney injury in high-risk patients."

	Source of funding: not reported	and/or a risk score ≥11) Exclusion criteria: 1) acute myocardial infarction; 2) acute pulmonary oedema; 3) cardiogenic shock; 4) dialysis; 5) multiple myeloma; 6) administration of sodium bicarbonate, theophylline, dopamine, mannitol, and/or fenoldopam; 7) recent (<48 hours) administration of iodinated contrast medium 8) enrolment in another study N total at baseline: Intervention: 146 Control: 146 Important prognostic factors[2]: Age ± SD: I: 76 ± 8		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.	Control: 3/147 (2%) 2 discontinued treatment 1 did not receive allocated treatment	need for dialysis) I: 16/146 (11%) C: 30/146 (21%) Odds ratio: 0.47, 95% CI 0.24 – 0.92 P<0.05	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 m2 (integer score 2 to 6), pre-existing anaemia(integer score 3), and CM volume (integer score 1 for each 100 cm3). The global scores ≥5, 6 to 10, 11 to 16, and _16 predict a CI-AKI risk of 7.5%, 14%, 26.1%, and 57.3%, respectively.

		C: 75 ± 9 Sex: I: 61% M C: 71% M eGFR ± SD: I: 32 ± 7 C: 32 ± 9 Groups comparable at baseline? Yes					
Marenzi, 2012	Type of study: randomised controlled trial Setting: elective and emergency patients Country: Italy Source of funding: not reported	Inclusion criteria: 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 angiography procedures requiring a direct renal injection of contrast,	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 coronary angiography. Matched hydration was continued throughout the catheterization procedure and for 4 h after the	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 oedema Incomplete outcome data: As described above)	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 I: 8% C: 18% P=0.052	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."

		2) cardiogenic shock, overt congestive heart failure, 3) acute respiratory insufficiency, 4) recent acute kidney injury, 5) chronic peritoneal or haemodialysis 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. N total at baseline: Intervention: 87 Control: 83 Important prognostic factors[2]: Age ± SD: I: 73 ± 7	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.				

		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 centres 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% C: 3.0% P=0.50	Authors' conclusion: "Controlled venous pressure guided fluid administration can safely and effectively reduce the risk of CIN in patients with CKD and chronic heart failure."
Usmiani, 2015	Type of study: randomized controlled trial	Inclusion criteria: 1) patients with chronic kidney disease (CKD)	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	Length of follow-up: 2 days	Outcome measures and effect size (include 95%CI and	Authors' conclusion: "In patients with CKD undergoing

	Setting: elective patients Country: Brazil Source of funding: not reported	undergoing coronary procedures Exclusion criteria: - N total at baseline: Intervention: 65 Control: 68 Groups comparable at baseline? Yes	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.	Standard saline and bicarbonate hydration	Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	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	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 reported	Inclusion criteria: 1) Eligible for both procedures 2) eGFR of less than 60 mL/min/1.73m2 Exclusion criteria: 1) primary PCI (emergency procedure); 2) cardiogenic shock; 3) acute heart failure; 4) end-stage renal disease on haemodialysis;	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, rate-matched with diuresis	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 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	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 mg/dL in 48 h or +50% in 7 days) I: 4 (6%) C: 16 (24%)	Authors' conclusion "Matched hydration was more effective than BS-NAC in CIAKI prevention."

		5) urinary tract infections within the last 3 months; 6) benign prostatic hyperplasia and; 7) previously known difficulties in urinary catheterization. Important prognostic factors2: 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		Plus: 1200mg p.o. N-acetylcysteine		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	572 RCTS 6 SRs new (177 SRs in earlier search strategy)

	"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	
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*)) 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)	103 obs.

	22 21 not 19 (134) – vanaf 2007: 105 – 103 uniek –in afzonderlijk document	

2.4.2 Statins and hydration against PC-AKI

Table of excluded studies

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

Evidence tables

Table of quality assessment for systematic reviews

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/not applicable	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 sub analysis, <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

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 assignment influences the process 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

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 efficacy of statins in	Describe intervention: A: Simvastin 40mg, 12	Describe control: A: Placebo	<u>End-point of follow-up (PC-AKI)</u>:	<u>Outcome measure-1</u>: PC-AKI, defined as an increase of ≥25%SCr or	<u>Facultative</u>: The result presented here involves a subgroup

[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	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	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	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	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>	analysis 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.

						(not reported in any of the included studies)	

Evidence table for intervention studies

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 haemodialysis), 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]: Age ± SD: I: 55 (6)	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.

		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 the procedure) were excluded.	Describe intervention (treatment/procedure/test): The rosuvastatin group received 10 mg every day for at least 48 hours before and 72 hours after CM administration.	Describe control (treatment/procedure/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 reported, but no post procedural adverse events occurred.	

		See article for a complete overview of exclusion criteria. N total at baseline: Intervention: 60 Control: 60 Important prognostic factors[2]: 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					
Abaci, 2015	Type of study: RCT Setting: University cardiology institute, inpatients Country: Turkey	Inclusion criteria: Patients naïve to statins and scheduled for coronary angiography with EGFR between 30 and 60 mL/min/1.73m^2. Exclusion criteria: Emergency coronary angiography, acute renal failure or end-stage renal	Describe intervention (treatment/procedure/test): Patients were given 40mg rosuvastatin <24 h before coronary angiography and hereafter 20mg/day for 2 days.	Describe control (treatment/procedure/test): No statin treatment	follow-up: Between 48-72h after angiography, 6 months and 1 year. Loss-to-follow-up: Intervention: 7 (6%) Reasons unknown Control: 5 (5%) 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 ≥25% from baseline <48 or72h after contrast exposure.	All patients received intravenous hydration with isotonic saline (14mL/kg/h, 0.9% sodium chloride) for 12h before and 24h after contrast exposure. Statistical analyses not clear. Secondary outcomes (death and

	Source of funding: not reported, no conflicts of interest	failure requiring dialysis. See article for a complete overview of exclusion criteria. N total at baseline: Intervention: 110 Control:110 Important prognostic factors[2]: 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)			Incomplete outcome data: See loss to follow-up	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	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	

2.4.3 Prophylactic NAC and hydration against PC-AKI

Table of excluded studies

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	Overlap 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 study (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	Overlap with Loomba, 2013 and is a less recent review
Burns, 2010	Not specifically patients with normal or abnormal kidney function (mix of impaired kidney function and diabetics)
Busch, 2013	Overlap 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 receive NAC)
Coyle, 2006	Not specifically patients with normal or abnormal kidney function (mix of impaired kidney function and diabetics)
Duong, 2005	Overlap 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 receive NAC)
Khalili, 2006	Prehydration only, not comparable to Dutch clinical practice
Kim, 2010	Already included in Loomba 2013
Kotlyar, 2005	Double with Kotlyar, 2005
Lee, 2011	Does not compare no NAC to NAC (both treatment arms receive NAC)
Liu, 2006	Overlap 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 research question broadly enough, used for cross referencing
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	Sub analysis of trial, observational data
Thiele, 2010	Already included in Loomba 2013
Trivedi, 2009	Overlap with Loomba, 2013 and is a less recent review
Zagler, 2006	Overlap with Loomba, 2013 and is a less recent review

Evidence tables

Risk of bias table for intervention studies

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	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear

	random numbers							
Jaffery, 2012	"Randomly assigned"	Unlikely	Unlikely	Unlikely	Unlikely	Likely	Unlikely	Unclear
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	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear

	randomization list							
Gulel, 2005	Random allocation table	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
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 assignment influences the process 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

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 centre Country: Taiwan Source of funding: non-commercial	Inclusion criteria: 1) all adult patients who received chest or abdominal contrast-enhanced computed tomography (CECT) Exclusion criteria: 1) patients undergoing long-term haemodialysis or peritoneal haemodialysis 2) patients who received another dose of contrast medium within 72 hours 3) patient refused to sign consent forms 4) patients had a known allergic reaction to N-acetylcysteine (NAC) N total at baseline: Intervention: 106 Control: 103 Important prognostic factors[2]: Age ± SD: I: 80 ± 9 C: 80 ± 11 Sex:	Describe intervention: 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: 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) Permanent renal replacement therapy: 0% in both groups	Authors' conclusion: "A single dose of NAC before CECT imaging can prevent CIN in an ED setting. However it does not improve mortality rate or the need for dialysis. Patients with congestive pulmonary oedema received an adjusted hydration schedule where the rates of fluid loading were decreased by 50%."

		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?					
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 informed consent <u>N total at baseline</u>:	Describe intervention: 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: 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 patients requiring CECT who had a moderate or high risk of CIN."

		Intervention: 36 Control: 35 <u>Important prognostic factors[2]</u>: 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-centre, elective patients Country:	<u>Inclusion criteria</u>: Patients with chronic kidney disease stage 1-4 undergoing elective computer-assisted tomography with non-ionic radiocontrast agents when compared to 0.45% saline alone <u>Exclusion criteria</u>:	Describe intervention: N-acetylcysteine 4800mg per os 0.45% saline, 1mL/kg/h over 24 hours	Describe control: 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 data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): No patients developed contrast induced acute kidney injury. There was no significant difference in serum creatinine change	Authors' conclusion: "Following radiocontrast administration neither vitamin E nor NAC in addition to saline demonstrated an additional beneficial effect on kidney fi=unction when compared to saline alone."

	Source of funding:	- N total at baseline: Intervention: 10 Control: 10 Important prognostic factors[2]: Age ± SD: mean: 75 years (not reported per group) Sex: 38% M (not reported per group) Groups comparable at baseline? Unclear				between the three study arms.	
Poletti, 2007	Type of study: randomized controlled trial Setting: emergency patients Country: Switzerland Source of funding: not reported	Inclusion criteria: 1) patients admitted consecutively to the emergency department during daytime hours 2) serum creatinine >1.2md/dL Exclusion criteria: 1) pregnancy 2) end stage renal failure with dialysis 3) suspicion of acute renal obstruction 4) asthma 5) severe cardiac failure 6) hemodynamically unstable condition	Describe intervention: 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 before CT 900mg NAC mixed into the 0.45% saline perfusion administered iv	Describe control: 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 placebo mixed into the 0.45% saline perfusion administered iv after completion of	Length of follow-up: 4 days Loss-to-follow-up: 7 (8%) 3 died, 3 left hospital 1 transferred to another hospital (not reported per group) Incomplete outcome data: 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."

		contraindicating iv hydration 7) nonurgent indications for CT N total at baseline: 87 Intervention: 44 Control: 43 Important prognostic factors[2]: Age ± SD: I: 70 ± 19 C: 73 ± 17 Sex: I: 59% M C: 67% M Groups comparable at baseline? Yes	after completion of CT at a rate of 1mL/kg body weight per hour for 12 hours	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 Source of funding: not reported	Inclusion criteria: 1) patients admitted consecutively to the emergency department 2) estimated creatinine clearance by MDRD of <60ml/min/1.73m^2 Exclusion criteria: 1) asthma 2) pregnancy 3) obstructive nephropathy 4) patient's refusal N total at baseline: 104 Intervention: 55	Describe intervention: 6000mg NAC iv diluted in 100mL saline, administered in the 60 minutes before the CT-scan Hydration of 250mL of 0.45% saline before CT-scan 1000mL saline 0.45% after CT-scan	Describe control: Placebo diluted in 100mL saline, administered in the 60 minutes before the CT-scan Hydration of 250mL of 0.45% saline before CT-scan	Length of follow-up: 10 days Loss-to-follow-up: Intervention: 3 (5%) Reasons not reported Control: 1 (2%) Reasons not reported Incomplete outcome data: As above	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 Composite event of death or acute kidney injury I: 33%	Authors' conclusion: "An ultra-high dose of intravenous NAC is ineffective at preventing nephrotoxicity in patients with renal impairment undergoing emergency contrast CT."

		Control: 59 Important prognostic factors[2]: Age ± SD: I: 78 ± 12 C: 78 ± 12 Sex: I: 49% M C: 51% M Groups comparable at baseline? Yes		1000mL saline 0.45% after CT-scan		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 Important prognostic factors[2]: Age ± SD: I: 66±11 C: 65 ± 15	Describe intervention: Acetylcysteine 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: 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."

		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 4) untreated gastrointestinal bleeding 5) previous treatment with theophylline, mannitol or nephrotoxic antibiotics	Describe intervention: 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: 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."

		N total at baseline: Intervention: 107 Control: 109 Important prognostic factors[2]: 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-centre inpatients, emergency procedure Country: United States of America	Inclusion criteria: 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 Exclusion criteria: 1) end stage renal disease requiring dialysis 2) hypersensitivity to NAC	Describe intervention: NAC: 1200mg bolus followed by 200mg/h for 24 hours In 500ml 5% dextrose solution of water iv Normal saline (0.9%) iv; 1/ml/kg for 24 hours	Describe control: Placebo in 500ml 5% dextrose solution of water iv Normal saline (0.9%) iv; 1/ml/kg for 24 hours	Length of follow-up: 72 hours for lab parameters 30 days for mortality and hospital stay 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 (=increase in serum creatinine concentration ≥25% above the baseline level within 72 hours of the administration of intravenous contrast) I: 16% C: 13% P=0.40	Patients with clinical evidence of heart failure received only NAC iv or placebo Authors' conclusion: "In acute coronary syndrome patients undergoing CAG with or without percutaneous intervention (PCI), high-dose intravenous NAC failed to reduce the incidence of CIN."

	Source of funding: not reported	3) history of life-threatening contrast reaction <u>N total at baseline</u>: Intervention: 192 Control: 206 <u>Important prognostic factors</u>[2]: 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				Outcomes of mortality and length of hospital not reported.	
Kim, 2010	Type of study: randomized controlled trial Setting: elective patients, one hospital Country: South Korea	<u>Inclusion criteria</u>: 1) patients scheduled for elective CAG and/or PCI with apparently normal renal function <u>Exclusion criteria</u>: 1) acute coronary syndrome requiring emergency CAG/PCI 2) cardiogenic shock	Describe intervention: Oral acetylcysteine 600mg twice a day on the day before and the day of coronary angiography 0.9% saline 1/mL/kg/h for 12	Describe control: 0.9% saline 1/mL/kg/h for 12 hours before and 6hours after CAG	<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 of at least 0.5mg/dL or >25% within 48 hours of contrast exposure) I: 3.8% C: 8.1% p>0.05	Authors' conclusion: "Not relevant – based on cystatin-C defined CIN results and not the sCR based CIN."

	Source of funding: not reported	3) iodinated contrast media administration within a month or 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 N total at baseline: Intervention: 80 Control: 86 Important prognostic factors[2]: 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 Groups comparable at baseline? Yes	hours before and 6hours after CAG				
Kinbara, 2010	Type of study: randomized controlled trial	Inclusion criteria: 1) Patients with stable coronary artery disease scheduled to undergo CAG	Describe intervention: NAC 704mg orally twice daily on the	Describe control: 0.9% saline iv 1/ml/kg/hour	Length of follow-up: 48 hours Loss-to-follow-up:	Outcome measures and effect size (include 95%CI and p-value if available):	Authors' conclusion: "These results suggest that both prophylactic NAC and aminophylline

	Setting: elective patients, one hospital Country: Japan Source of funding: not reported	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 haemodialysis 5) planned post-contrast dialysis 6) allergies to the 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[2]</u>: Age ± SD: I: 70 ± 10 C: 70 ± 8 Sex: I: 80% M C: 80% M SCr (mg/dL)	day before and 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	For 30 minutes before and 10 hours after angiography	Not reported <u>Incomplete outcome data</u>: Not reported	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	administration are effective in preventing CIN, but not with hydration alone.”

		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 centre 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]: Age ± SD: I: 72 ± 12 C: 69 ± 12 Sex: I: 59% M C: 69% M SCr (µmol/L) I: 110 ± 42 C: 124 ± 63 Groups comparable at baseline? Yes	Describe intervention: 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: 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."

Sadat, 2011	Type of study: randomized controlled trial Setting: elective patients, single centre 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]: 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 day 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 Setting: emergency patients, single centre	Inclusion criteria: 1) patients admitted for ST-segment elevation acute myocardial infarction treated with primary PCI Exclusion criteria: 1) dialysis 2) known allergy to NAC 3) inability to take NAC orally	Describe intervention: NAC 705mg orally before and 12, 24, 26 pours after intervention (2.8g in total) Hydration with iv Ringer lactate	Describe control: Hydration with iv Ringer lactate solution at a rate of 1-2ml/kg/hour for more than 12 hours after primary CAG	Length of follow-up: 36 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 in sCr level of 25% or more from baseline value within 72 hours after primary angioplasty) I: 2/38 (5%)	Authors' conclusion: "While N=acetylcysteine might have the possibility 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

	Country: Japan Source of funding: not reported	 N total at baseline: Intervention: 38 Control: 38 Important prognostic factors[2]: 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	solution at a rate of 1-2ml/kg/hour for more than 12 hours after primary CAG			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.	significantly different between the two groups."
Thiele, 2010	Type of study: randomized controlled trial Setting: emergency patients, one tertiary hospital Country: Germany	Inclusion criteria: 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-cordial leads Exclusion criteria: 1) previous fibrinolysis <12 hours 2) known NAC allergy 3) chronic dialysis 4) pregnancy	Describe intervention: NAC intravenous bolus 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	Describe control: 10mL of 0.9% saline at each injection Hydration with intravenous 0.9% saline; infusion rate 1ml/kg/hour for 12 hours (or 0.5mg/kg/h in overt heart failure)	Length of follow-up: Laboratory parameters: 72 hours Clinical endpoints: 6 months Loss-to-follow-up: none Incomplete outcome data: 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) 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	Authors' conclusion: "High-dose iv NAC does not provide additional clinical benefit to placebo with respect to CIN in non-selected patients undergoing angioplasty with moderate doses of contrast medium and optimal hydration."

	Source of funding: not reported	5) contra-indications for magnetic resonance imaging <u>N total at baseline</u>: Intervention: 126 Control: 125 <u>Important prognostic factors</u>[2]: 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	0.5mg/kg/h in overt heart failure)			New congestive heart failure I: 11/126 (9%) C: 7/125 (6%) p>0.05	
CAG or PCI, decreased kidney function							
ACT, 2011	Type of study: randomized controlled trial Setting: inpatients, elective, multi-centre	<u>Inclusion criteria</u>: 1) patients undergoing 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	Describe intervention: NAC 2x600mg orally every 12 hours for 2 days (2 doses before and 2 doses after contrast administration, total dose 4800mg)	Describe control: placebo orally every 12 hours for 2 days (2 doses before and 2 doses after contrast administration)	<u>Length of follow-up</u>: 48-96 hours for laboratory parameters 30 days for clinical events <u>Loss-to-follow-up</u>: Intervention: 56 (5%) 12 did not receive study drug before angiography	Outcome measures and effect size (include 95%CI 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%)	Authors' conclusion "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

	Country: Brazil Source of funding: non-commercial	-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 factors[2]</u>: Age ± SD: I: 68 ± 10 C: 68 ± 10 Sex: I: 62% M C:61 % M	Hydration with 0.9% saline 1mg/kg/hour from 6-12 hours before to 6-12 hours after angiography	Hydration with 0.9% saline 1mg/kg/hour from 6-12 hours before to 6-12 hours after 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>: Intervention: 1153 (98%) had data included in laboratory parameters analysis 1171 (99.9%) had data included in secondary outcome analysis Reasons not reported	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: 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)	coronary or peripheral vascular angiography.”

		Groups comparable at baseline? Yes			Control: 1119 (98%) had data included in laboratory parameters analysis 1135 (99.9%) had data included in secondary outcome analysis Reasons not reported	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	<u>Inclusion criteria</u>: 1) patients undergoing CAG and/or PCI 2) age ≥18 years 3) stable sCr ≥1.2mg/dL <u>Exclusion criteria</u>: 1) sCr >4mg/dL 2) a history of dialysis, multiple myeloma, pulmonary oedema, 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 contrast media or NAC 6) previous enrolment in the same or other protocols 7) administration of mannitol, theophylline, dopamine, dobutamine, nonsteroidal anti-	Describe intervention: 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: 0.9% saline iv 1ml/kg/hour for 12 hours before and 12 hours after contrast administration	<u>Length of follow-up</u>: 5 days <u>Loss-to-follow-up</u>: none <u>Incomplete outcome data</u>: 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 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.	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."

		inflammatory drugs or fenoldopam N total at baseline: Intervention: 52 Control: 51 Important prognostic factors[2]: 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					
Ferrario, 2009	Type of study: randomized controlled trial Setting: elective patients, university hospital Country: Italy	Inclusion criteria: 1) patients scheduled for elective or diagnostic CAG and/or PCI 2) age ≥18 years 3) creatinine clearance <55ml/min and a stable renal function Exclusion criteria: 1) ongoing acute myocardial infarction or acute coronary syndrome	Describe intervention: 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	Describe control: 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	Length of follow-up: 3 days Loss-to-follow-up: Intervention: 4 (4%) Reasons not reported Control: 4 (3%) Reasons not reported Incomplete outcome data:	Outcome measures and effect size (include 95%CI and p-value if available): CIN (=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	Authors' conclusion "In our experience, NAC did not prevent CIN in patients receiving iso-osmolar (iodixanol) contrast media and adequate hydration."

	Source of funding: not reported	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]: Age ± SD: I: 75 ± 8 C: 75 ± 7 Sex: I: 68% M C: 62% M Creatinine clearance (mL/min) I: 37 ± 11.5 C: 40 ± 9.3 Groups comparable at baseline? Yes	hours before the procedure and 24 hours after	hours before the procedure and 24 hours after	Not reported		
Gulel, 2005	Type of study: randomized	<u>Inclusion criteria</u>: 1) patients scheduled for elective diagnostic CAG	Describe intervention:	Describe control:	<u>Length of follow-up</u>: 48 hours	Outcome measures and effect size (include 95%CI and p-value if available):	Authors' conclusion: "Our results show that oral acetylcysteine does

	controlled trial Setting: elective, single centre Country: Turkey Source of funding: not reported	2) chronic renal impairment: 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[2]</u>: Age ± SD: I: 61 ± 12 C: 62 ± 12 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	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	0.9% saline 1ml/kg/h in 12 hours before the procedure and 12 hours after	<u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	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	not reduce the risk of contrast nephropathy when used before elective diagnostic CAG in patients with renal dysfunction."

Habib, 2016	Type of study: randomized controlled trial Setting: European Gaza Hospital, Gaza, Palestine (Israel) Source of funding: not reported	Inclusion criteria: 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) Exclusion criteria: Not stated N total at baseline: Group A: 40 Group C: 40 Important prognostic factors[2]: Age ± SD: Group A: 63 ± 8 Group C: 63 ± 8 Sex: Group A: 67% M Group C: 76% M Groups comparable at baseline? Yes	Describe intervention: 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: 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	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 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."
Izani Wan, 2008 (Mohamed)	Type of study: randomized controlled trial Setting: elective patients, single centre	Inclusion criteria: 1) patients electively admitted for CAG 2) calculated creatinine clearance 40-90ml/min 3) age ≥18 years Exclusion criteria: 1) severe renal failure	Describe intervention: NAC 600mg orally every 12 hours for 2 days (2 doses on the day before and 2 doses on the day of	Describe control: 0.45% saline 1ml/kg/h in 12 hours before the procedure and 12 hours after	Length of follow-up: 48 hours Loss-to-follow-up: Intervention: 4 (8%) 1 early discharge 2 procedure cancellation 1 procedure complication	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%)	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

	Country: Malaysia Source of funding: not reported	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]: Age ± SD: I: 58 ± 8 C: 56 ± 7 Sex: I: 86% M C: 82% M SCr (µmol/L) I: 124 ± 17 C: 124 ± 22 Groups comparable at baseline? Yes	contrast administration, total dose 2400mg) 0.45% saline 1ml/kg/h in 12 hours before the procedure and 12 hours after		Control: 4 (7%) 2 early discharge 2 procedure cancellation <u>Incomplete outcome data</u>: As above	C: 6/51 (12%) P=0.27 None of the patients who developed CIN required dialysis.	impairment undergoing elective CAG."
Koc, 2012	Type of study: randomized controlled trial Setting: elective	<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	Describe intervention: NAC 600mg intravenously every 12 hours for 2 days	Describe control: 0.9% saline iv 1ml/kg/h in on the day before, on the day of, and on the	<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 (=baseline sCr ≥25% and/or an absolute increase in sCr of ≥0.5	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

	patients, single centre Country: Turkey Source of funding: not reported	 Exclusion criteria: 1) contrast-agent hypersensitivity 2) pregnancy or lactation 3) decompensated heart failure 4) pulmonary oedema 5) emergency catheterisation 6) acute or end-stage renal failure N total at baseline: Intervention: 80 Control: 80 Important prognostic factors[2]: Age ± SD: I: 62 ± 10 C: 65 ± 11 Sex: I: 76% M C: 79% M Creatinine clearance (mL/min) I: 59 ± 16 C: 58 ± 16 Groups comparable at baseline? Yes	(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	day after the procedure	Incomplete outcome data: Not reported	mg/dL 48 hours after the procedure) I: 2 (3%) C: 13 (16%) P=0.006 No patients needed haemodialysis.	the protection of renal function in patients with mild to moderate renal dysfunction who are undergoing CAG and/or PCI.”
Kotlyar, 2005	Type of study: randomised	Inclusion criteria:	Describe intervention:	Describe control:	Length of follow-up: 2-4 days and 30 days	Outcome measures and effect size (include 95%CI and p-value if available):	Authors’ conclusion: “For day-stay patients with mild to moderate

	controlled trial Setting: elective patients admitted for 1 day Country: Australia Source of funding: commercial (pharmaceutical company)	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[2]</u>: Age ± SD: I1: 66 ± 14 I2: 67 ± 12 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	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 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	Hydration iv: 0.9% saline 100ml/hour 2 hours before procedure and 5hours after procedure	<u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	None of the patients developed CIN. None of the patients developed a need for dialysis.	renal impairment 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.”

		Groups comparable at baseline? Yes					
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	Inclusion criteria: 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 Exclusion criteria: Patients with acute renal failure, end-stage 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, 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. N total at baseline: NAC: 35 Placebo: 30	Describe intervention: NAC + NS: Group of patients who received NS and NAC	Describe control: Placebo + NS: Group of patients who received NS only	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, 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."

		Important prognostic factors[2]: 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: Canada Source of funding: not reported	Inclusion criteria: 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 sCr≥1.3mg/dL for females 4) age ≥18 years Exclusion criteria: 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	Describe intervention: 600mg NAC orally four doses in total (1 before procedure and 3 after every 12 hours) Iv hydration 0.45% saline1ml/kg/hour 4-6 hours before and 12 hours after procedure	Describe control: Iv hydration 0.45% saline1ml/kg/hour 4-6 hours before and 12 hours after procedure	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 (=increase in sCr >44µmol/L (0.5mg/dL) and/or 25% above baseline within 48 hours) I: 1/20 (5%) C: 2/20 (10%) p<0.05 No patients required dialysis therapy.	Authors' conclusion "These results suggest that this cohort gained no added protection to renal function with the use of NAC."

		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]: Age ± SD: I: 76 ± 6 C: 75 ± 10 Sex: I: 60% M C: 70% M Groups comparable at 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

2.4.4 Vitamin C and hydration against PC-AKI

Table of excluded studies

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 pentoxifylline 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

Evidence tables

Table of quality assessment for systematic reviews

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/ not applicable	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

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 assignment influences the process 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

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: Not reported	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: N A: 238 B: 143	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, oral 0.5g on the night of	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] favouring 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: 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 outcome measure)

		C: 212 D: 174 E: 70 F: 520 G: 149 H: 243 I:202 Groups comparable at baseline? Unclear	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 acid, 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			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

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 factors[2]: Age ± SD: I: 71 ± 9	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."

		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	<u>Inclusion criteria:</u> 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. <u>Exclusion criteria:</u> 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 disease 5) undergone catheter procedures involving the	Describe intervention: 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 group.	Describe control: 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	<u>Length of follow-up:</u> 3 days <u>Loss-to-follow-up:</u> <u>Intervention:</u> None reported Reasons: not applicable <u>Control:</u> None reported Reasons: not applicable <u>Incomplete outcome data:</u> 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."

		use of a contrast agent within the previous 48 h <u>N total at baseline:</u> Intervention: 218 Control: 211 <u>Important prognostic factors2:</u> <u>age ± SD:</u> I: 73 ± 10 C: 74 ± 10 <u>Sex:</u> I: 79% M C: 82% M Groups comparable at 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

Literature search strategy

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)						

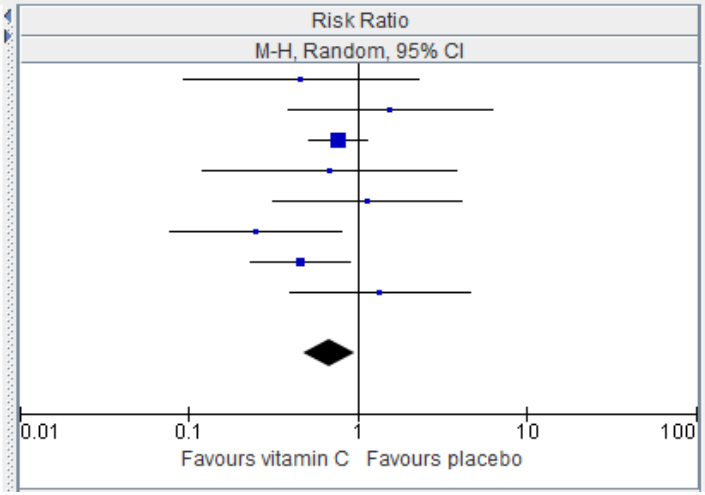
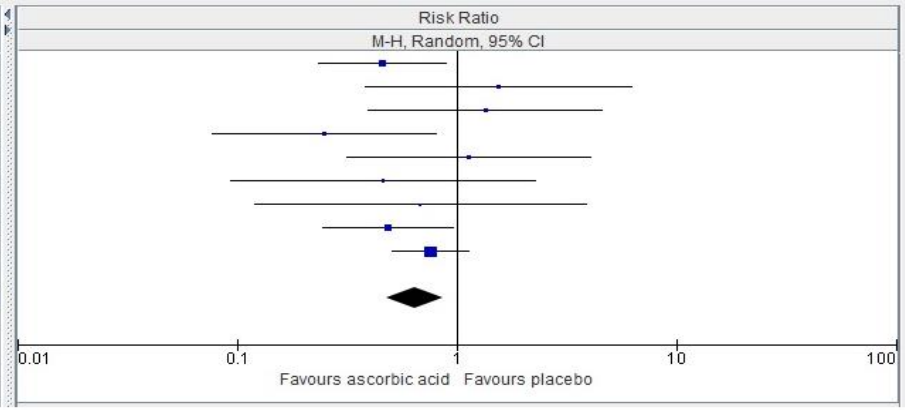


Figure 7.10 Meta-analysis including all RCTs on vitamin C (both impaired kidney function and kidney function not reported)

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)						



2.4.5 Nephrotoxic medication and PC-AKI

Table of excluded studies

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 fulfil selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Cirit, 2006	Does not fulfil selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Del Veccio	Narrative review
Diogo, 2010	Does not fulfil selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Duan, 2015	Does not fulfil 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 fulfil selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Gu, 2013	Does not fulfil 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 fulfil 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
Kalyesubula, 2014	Narrative review
Kellum, 2001	Does not fulfil selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Kiski, 2010	Does not fulfil selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Lapi, 2014	Does not fulfil selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Li, 2011	Does not fulfil selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Li, 2012	Narrative review
Li, 2012b	Only abstract available
Marenzi, 2012	Does not fulfil 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 fulfil 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 fulfil 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 fulfil 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 fulfil 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 fulfil 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 fulfil 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 fulfil selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Umruddin, 2012	Does not fulfil 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 fulfil selection criteria (nephrotoxic medication is not stopped prior to radiological examination with intravasal contrast)
Zhou, 2013	Narrative review

Evidence tables

Risk of bias table for intervention studies

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 interactive voice-response system	Unlikely	Unlikely	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 assignment influences the process 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

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 Control: 102 Important prognostic factors[2]: Age ± SD:	Describe intervention: 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, intravenous normal saline at 1 mL/kg/hour during contrast exposure and 6 hours after the procedure or until discharge.	Describe control: No discontinuation of angiotensin II blockade medication Intravenous normal saline at 3 mL/kg/hour for at least an hour before contrast injection, intravenous 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 for cardiovascular cause: I: 0 (0%) C: 3 (2%)	"Contrast induced AKI defined as an absolute rise 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."

		I: 73 ± 9 C: 72 ± 8 Sex: I: 74% M C: 73 % M Groups comparable at baseline? yes					
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 factors[2]: unclear Age ± SD: I: C: Sex: I: % M C: % M	Describe intervention: 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: 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 data: unclear Intervention: N (%) Reasons (describe) Control:	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."

		Groups comparable at baseline? Incidence of diabetes and hypertension was significantly lower in the ACE-naïve group			N (%) Reasons (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

Literature search strategy

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	

2.4.6 Prophylactic renal replacement against PC-AKI

Table of excluded studies

Table: Exclusion after revision of full text

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

Evidence tables

Table of quality assessment for systematic reviews

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/not applicable	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

Notes

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

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

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 assignment influences the process 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

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Cruz, 2012	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	Inclusion criteria SR: 1) studies that evaluated 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*	Describe intervention: A: haemodialysis (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 Prehydration 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] favouring 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] favouring RRT. Heterogeneity (I^2): 36%	<u>Facultative</u>: Author's conclusion: "In this updated meta-analysis periprocedural 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 heterogeneity of included studies

	F: Randomized 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	*cohort 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 Groups comparable at baseline? Unclear				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] favouring 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] favouring RRT. Heterogeneity (I^2): 19% <u>Outcome measure-4</u> Mortality Not reported per study. Pooled analysis for 5 studies. I: 2.6% 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

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 Important prognostic factors[2]:	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%) P0.009 Cardiovascular deaths:	"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."

		Age ± SD: I: 73 ± 11 C: 74 ± 8 Sex: I: 84% M C: 67% M Groups comparable at baseline? Yes				I: 0/25 (0%) C: 5/21 (24%) p-value not reported	

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-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	

2.4.7 Nephrotoxicity of GBCA

Knowledge gaps
The incidence of PC-AKI after administration of GBCA is unknown.
The difference in nephrotoxic potential between different GBCA's is unknown.

Indicators
None.

Implementation

Recommendation	Time frame for implementation: <1 year, 1 to 3 years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
Use the lowest dose GBCA needed to achieve a diagnostic MRI examination.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
Do not use prophylactic measures to avoid the development of PC-AKI in high risk patients (eGFR<30ml/min/1.73m^2) receiving GBCA intravenously at the appropriate dose.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
Do not substitute ICM with GBCA in order to avoid PC-AKI in computed tomography and/or digital subtraction angiography.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.
[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.
[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be**.**

Table of excluded studies

Table of Exclusions after reading full text

Author and year	Reason of exclusion
Belling 2002	Does not fulfil selection criteria. No control group. Descriptive.
Cochran 2002	Does not fulfil selection criteria. No control group. Descriptive.
Cohan 1997	Does not fulfil selection criteria. No control group. Descriptive.
Conner 2017	Does not fulfil selection criteria. No control group. Descriptive.
Conner 2017	Does not fulfil selection criteria. No control group. Descriptive.
Davenport 2012	Does not fulfil selection criteria. No control group. Descriptive.
Ding 2018	Does not discuss treatment of extravasation
Ding 2018	Does not fulfil selection criteria. No control group. Descriptive.
Earhart 2011	Does not fulfil selection criteria. No control group. Descriptive.

Fallscheer 2007	Does not fulfil selection criteria. No control group. Descriptive.
Kim 2017	Does not fulfil selection criteria. No control group. Descriptive.
Kim 2017	Does not fulfil selection criteria. No control group. Descriptive.
Nicola 2016	Does not fulfil selection criteria. No control group. Descriptive.
Rose 2015	Does not fulfil selection criteria. No control group. Descriptive.
Sbitany 2010	Does not fulfil selection criteria. No control group. Descriptive.
Schaverien 2008	Does not fulfil selection criteria. No control group. Descriptive.
Schummer 2010	Does not fulfil selection criteria. No control group. Descriptive.
Sonis 2017	Does not fulfil selection criteria. No control group. Descriptive.
Sonis 2017	Does not fulfil selection criteria. No control group. Descriptive.
Sum 2006	Does not fulfil selection criteria. No control group. Descriptive.
Tonolini 2012	Does not fulfil selection criteria. No control group. Descriptive.
Tonolini 2016	No comparison therapies. Letter to the editor on the occasion of Nicola 2016
Tsai 2007	Does not fulfil selection criteria. No control group. Descriptive.
Vandeweyer 2000	Does not fulfil selection criteria. No control group. Descriptive.
Wang 2007	Does not fulfil selection criteria. No control group. Descriptive.
Wilson 2011	Does not fulfil selection criteria. No control group. Descriptive.

Search strategy

Database	Search terms	Total
PubMed 1996 – februari 2018	(("Extravasation of Diagnostic and Therapeutic Materials"[Mesh] OR extravasation* [tiab] OR compartment syndrome*[tiab]) AND ("Contrast Media"[Majr] OR contrast medi*[ti])) AND (("1996/01/01"[PDat] : "3000/12/31"[PDat]) AND (English[lang] OR Dutch[lang])) *Systematic Review filter:* (systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR "cochrane database syst rev"[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR "research synthesis"[tiab] OR "research integration"[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT "psycinfo database"[tiab]) OR pubmed[tiab] OR scopus[tiab] OR "web of science"[tiab] OR "data synthesis"[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR "meta-analysis as topic"[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt]) *RCT filter:* ((random*[tiab] AND (controlled[tiab] OR control[tiab] OR placebo[tiab] OR versus[tiab] OR versus[tiab] OR group[tiab] OR groups[tiab] OR comparison[tiab] OR compared[tiab] OR arm[tiab] OR arms[tiab] OR crossover[tiab] OR cross-over[tiab]) AND (trial[tiab] OR study[tiab])) OR ((single[tiab] OR double[tiab] OR triple[tiab]) AND (masked[tiab] OR blind*[tiab]))) OR ((random*[ot] AND (controlled[ot] OR control[ot] OR placebo[ot] OR versus[ot] OR versus[ot] OR group[ot] OR groups[ot] OR comparison[ot] OR compared[ot] OR arm[ot] OR arms[ot] OR crossover[ot] OR cross-over[ot]) AND (trial[ot] OR study[ot])) OR ((single[ot] OR double[ot] OR triple[ot]) AND (masked[ot] OR blind*[ot]))) = 319	480
Embase (Elsevier)	(('extravasation'/exp OR extravasation*:ab,ti OR 'compartment syndrom*':ab,ti) AND ('contrast medium'/exp/mj OR 'contrast medi*':ti) AND ([dutch]/lim OR [english]/lim) AND [1996-2018]/py) NOT 'conference abstract':it)) *Systematic Review filter*: (('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo: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))) *RCT filter*: (('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)) = 319	

3. Hypersensitivity reactions

3.1 Introduction to hypersensitivity reactions

-

3.2 Definitions of adverse drug reactions

-

3.3 Management of acute hypersensitivity reactions

Knowledge Gaps

It is unclear which treatments of acute hypersensitivity reactions after CM administration lead to a higher severity of complaints. The following outcomes would be relevant to study: duration of acute reaction, morbidity, mortality, costs, hospitalization in an IC-unit, length of stay.

Quality Assurance Indicators

Every hospital needs a local protocol for management of acute hypersensitivity reactions after CM administration, accessible in all rooms where CM are administered.

1. Hospital-wide protocols for management of acute hypersensitivity reactions after CM administration, accessible in all rooms where CM are administered	
Operationalization	Is there an overall hospital-wide protocol or process-agreement for management of acute hypersensitivity reactions after CM administration? And is this protocol accessible in all rooms where CM is administered?
Numerator	Not applicable
Denominator	Not applicable
Type of indicator	Input
In- and exclusion criteria	Inclusion A hospital-wide protocol for management of acute hypersensitivity reactions after CM administration. This protocol is accessible in all rooms where CM is administered.
Quality domain	Safety and effectivity
Measuring frequency	Once a year
Report year	2020
Frequency of report	Once a year

Medication for treatment of acute reactions after CM administration should be available in every room where CM is administered.

2. Hospital-wide protocols about prevention of PC-AKI	
Operationalization	Is there medication for treatment of acute reactions after CM administration available in every room where CM is administered?
Numerator	Not applicable
Denominator	Not applicable
Type of indicator	Input
In- and exclusion criteria	Inclusion Medication for treatment of acute reactions after CM administration available in every room where CM is administered. As a minimum the following medication should be available: adrenaline, salbutamol, H1-antihistamine (clemastine) IV, corticosteroid IV.
Quality domain	Safety and effectivity
Measuring frequency	Once a year
Report year	2020
Frequency of report	Once a year

Implementation of Recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation	Actions needed for implementation	Parties responsible for actions[3]	Other remarks
Preparation: Have the drugs (as a minimum requirement: adrenaline, salbutamol, H1-antihistamine (clemastine) IV, and corticosteroid IV (e.g. prednisolone)), equipment and protocol for treatment of an acute adverse reaction readily available in every room where contrast agents are administered. Adhere to local protocols for accessibility of a resuscitation and emergency response team. Keep every patient with an acute hypersensitivity reaction to CM in a medical environment for at least 30 minutes after contrast agent injection. Moderate and severe reactions need a prolonged observation.	1 to 3 years	None	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Dissemination of guideline, development of local protocols for treatment of acute hypersensitivity reactions after CM	NVvR, NVVC	
Acute management general principles: Check and stabilize patient according to the ABCDE method Stop infusing contrast agent and replace IV line with crystalloid. Dyspnoea or stridor: let patient sit up Hypotension: keep patient in prone position, raise legs Consider measuring serum tryptase (see recommendations in chapter Laboratory Diagnosis of Hypersensitivity Reactions to Contrast Media) Record acute allergic reactions in allergy registry (see chapter Organization of Healthcare)	1 to 3 years	None	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Spreading knowledge of guideline, development of local protocols for treatment of acute hypersensitivity reactions after CM	NVvR, NVVC	

Note: After administration of clemastine the patient may no longer be able (or insured) to drive a car/motorcycle or to operate machinery.							
Severe reactions: Cardiac or respiratory arrest: Start CPR Call the CPR team. Anaphylactic reaction or stridor: Call rapid response team (SIT-team) Give oxygen 10-15L/min with non-rebreathing mask Give 0.5mg adrenaline IM in lateral upper thigh Give fluid bolus of crystalloid 500ml IV in 10 minutes, repeat as necessary. Consider nebulizing with salbutamol 5mg or budesonide 2mg for stridor Give clemastine 2mg IV Consider adding corticosteroid (e.g. prednisolone 50mg iv, *)	1 to 3 years	None	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Spreading knowledge of guideline, development of local protocols for treatment of acute hypersensitivity reactions after CM	NVvR, NVVC	
Moderate reactions: Consider transferring the patient to a department with facilities for monitoring of vital functions. Isolated bronchospasm: Salbutamol 2.5-5mg nebulization in oxygen by facemask 10-15 L/min (nebulization is easier to administer and more effective than dose aerosol). In mild cases asthma patients may use their own salbutamol dose aerosol. In case of deterioration give adrenaline 0.5mg IM and consider call rapid response team Isolated facial oedema without stridor: Give oxygen 10-15L/min via anon-rebreathing mask Give clemastine 2mg IV If oedema is severe or near airways or if stridor develops: treat as anaphylaxis	1 to 3 years	None	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Spreading knowledge of guideline, development of local protocols for treatment of acute hypersensitivity reactions after CM	NVvR, NVVC	

Isolated urticaria/diffuse erythema: Give clemastine 2mg IV If accompanied by hypotension: treat as anaphylaxis Isolated hypotension: Give bolus of crystalloid 500ml IV, repeat as necessary. If accompanied by bradycardia, consider atropine 0.5mg IV If accompanied by other symptoms: treat as anaphylaxis							
Mild reactions: General: Mild reactions may only need reassurance Observe vital signs until symptoms resolve Do not remove iv access during observation Consider: Prescribing a non-sedating antihistamine, e.g. desloratadine 5mg PO (once daily) for mild allergic reactions Ondansetron 4mg IV for protracted vomiting	1 to 3 years	None	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Spreading knowledge of guideline, development of local protocols for treatment of acute hypersensitivity reactions after CM	NVvR, NVVC	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.
[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.
[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Evidence Tables

Not applicable.

Table of excluded studies

After full text review

Author and year	Reasons for exclusion
Boyd, 2017	Narrative review. No control arm
Brockow, 2011 20	Narrative review. No control arm
Bush, 1991	Patient group not treated with CM. Does not cover treatment
Cochran, 2005	Expert opinion
Cohan, 1996	Narrative review.
Collins, 2009	Narrative review. No control arm.
Coors, 2006	Narrative review. No control arm.
Davis, 2015	Narrative review. No control arm
Dawson, 2002	Narrative review. No control arm. Does not cover treatment
Drain, 2001	Narrative review. No control arm.
Hash, 1999	Narrative review. No control arm
Hollingswerth, 1991	Patient group not treated with CM
Iyer, 2013	Narrative review. No control arm.
Kounis, 2015	Narrative review. No control arm
Liebhart, 2007	Narrative review. No control arm. Patient group not treated with CM
Marycz, 2014	Narrative review. No control arm
Masch, 2016	Narrative review. No control arm
Meth, 2006	Narrative review. No control arm.
Morcos, 2001	Narrative review. No control arm.
Morcos, 2005	Expert opinion
Morcos, 2005	Narrative review. No control arm.
Morcos, 2006	Narrative review. No control arm.
Morzycki, 2017	Narrative review. No control arm
Namasivayam, 2006a	Narrative review. No control arm. Patient group not treated with CM
Namasivayam, 2006b	Narrative review. No control arm.
Nandwana, 2015	Narrative review. No control arm. Patient group not treated with CM
Nayak, 2009	Narrative review. No control arm.
Newmark, 2012	Narrative review. No control arm
Petscavage, 2012	Patient group not treated with CM
Pumphrey, 2004	Narrative review. No control arm.
Ring, 2010	Narrative review. Patient group not treated with CM
Rose, 2015	Narrative review
Sadler, 1994	Patient group not treated with CM
Seikh, 2013	Expert opinion. Patient group not treated with CM
Shellock, 1993	Patient group not treated with CM
Skowronski, 1987	Patient group not treated with CM
Szebeni, 2004	Narrative review. No control arm.
Thompsen 1998b	Narrative review. No control arm.
Thompsen, 1998a	Narrative review. No control arm.
Thompsen, 2004	More recent guideline available
Thompsen, 2016	Narrative review. No control arm
Toncic, 2009	Narrative review. No control arm. Patient group not treated with CM
Toogood, 1987	Patient group not treated with CM
Wang, 2008	Narrative review. No control arm.
Wang, 2014	No comparison between effectivity of several treatments
Winbery, 2002	Narrative review. No control arm.
Wolkenstein, 1995	Narrative review. No control arm. Patient group not treated with CM

Literature Search

Database	Search String	Total
PubMed 1985 – december 2017	("Contrast Media"[Mesh] OR contrast medi* [tiab] OR contrast agent* [tiab] OR contrast material* [tiab] OR contrast dose [tiab] OR contrast doses [tiab] OR contrast dosage [tiab] OR radiocontrast medi* [tiab] OR radiocontrast agent* [tiab] OR radiopaque medi* [tiab] OR radiocontrast dose [tiab] OR radiocontrast doses [tiab] OR radiocontrast dosage [tiab] OR "Barium"[Mesh] OR barium [tiab] OR gadolinium [tiab] OR microbubble* [tiab])	328

	AND (("Drug Hypersensitivity"[Mesh] OR hypersensitiv* [tiab] OR allergic* [tiab] OR anaphylaxis [tiab] OR anaphylact* [tiab] OR adverse reaction*[tiab] OR urticaria* [tiab] OR diffuse erythema [tiab] OR facial edema [tiab] OR angioedema [tiab] OR bronchospasm* [tiab] OR laryngeal edema [tiab] OR anaphylactic shock [tiab] OR hypotension [tiab] OR pulmonary edema [tiab] OR cardiac arrest [tiab] OR respiratory arrest [tiab]) AND (acute [tiab] OR after administration [tiab] OR rapid* [tiab] OR severe [tiab])) AND (treatment [tiab] OR treat [tiab] OR recommend* [tiab]) AND ("english"[Language]) AND ("1985"[Date - Publication] : "3000"[Date - Publication]) = 215	
Embase (Elsevier)	contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp/mj OR barium:ab,ti OR 'gadolinium'/exp/mj OR gadolinium:ab,ti OR 'microbubble'/exp/mj OR microbubble*:ab,ti) AND (('hypersensitivity'/exp OR hypersensitiv*:ab,ti OR allergic*:ab,ti OR anaphylaxis:ab,ti OR anaphylactic:ab,ti OR 'adverse reaction*':ab,ti OR urticaria*:ab,ti OR 'diffuse erythema':ab,ti OR 'facial edema':ab,ti OR angioedema:ab,ti OR bronchospasm:ab,ti OR 'laryngeal edema':ab,ti OR 'anaphylactic shock':ab,ti OR hypotension:ab,ti OR 'pulmonary edema':ab,ti OR 'cardiac arrest':ab,ti OR 'respiratory arrest':ab,ti) AND (acute:ab,ti OR 'after administration':ab,ti OR rapid*:ab,ti OR severe:ab,ti)) AND (treatment:ab,ti OR treat:ab,ti OR recommend*:ab,ti)) AND [english]/lim AND [1985-2018]/py NOT 'conference abstract':it NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) = 282 (279 unique)	

3.4 Treatment of late reactions to CM

Knowledge Gaps
It is unclear whether any treatment of late hyper sensitivity reactions after contrast administration leads to a quicker recovery, a less serious course, sequelae, mortality, morbidity hospitalization. It is also not clear whether one treatment options might lead to a better outcome (as described in the previous sentence) compared to another.

Quality Assurance Indicators
None.

Implementation of Recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
Warn patients who have had a previous hypersensitivity reaction to contrast media, that a late hypersensitivity reaction may be possible, usually a skin reaction.	1 to 3 years	None	Lack of knowledge of guideline. Lack of experience for recognizing late hypersensitivity reactions after contrast administrations.	Lack of knowledge of guideline.	Disseminations of guideline	NVvR	
Patients should contact their general practitioner if they have a late hypersensitivity reaction after CM administration. Consider informing the radiology department about the occurrence and symptoms of a late hypersensitivity reaction after CM administration.	1 to 3 years	None	Lack of knowledge of guideline. Lack of experience for recognizing late hypersensitivity reactions after contrast administrations.	Lack of knowledge of guideline.	Disseminations of guideline	NVvR	
When the symptoms of a late hypersensitivity reaction are mild, a wait-and-see approach can be justified.	1 to 3 years	None	Lack of knowledge of guideline. Lack of experience for recognizing late hypersensitivity reactions after contrast administrations.	Lack of knowledge of guideline.	Disseminations of guideline	NVvR	
Treat late hypersensitivity reactions symptomatically. Consider treatment of skin reactions with oral or topical corticosteroids.	1 to 3 years	None	Lack of knowledge of guideline. Lack of experience for recognizing late hypersensitivity reactions after contrast administrations.	Lack of knowledge of guideline.	Disseminations of guideline	NVvR	
When severe symptoms develop, such as generalized pustulosis or painful cutaneous blisters, refer the patient to a dermatologist.	1 to 3 years	None	Lack of knowledge of guideline. Lack of experience for recognizing late hypersensitivity reactions after contrast administrations.	Lack of knowledge of guideline.	Disseminations of guideline	NVvR	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.

[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, etcetera.

[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Evidence Tables

Not applicable.

Table of excluded studies

Author and Year	Reason for exclusion
Bellin (2011)	Does not fulfil selection criteria. No control group. Descriptive.
Brockow K (2011)	Does not fulfil selection criteria. No control group. Descriptive.
Christiansen C (2000)	Does not fulfil selection criteria. No control group. Descriptive.
Egbert (2014)	Does not fulfil selection criteria. No control group. Descriptive.
Fok (2017)	Does not fulfil selection criteria. No control group. Descriptive.
Goksel (2011)	Does not fulfil selection criteria. No control group. Descriptive.
Hasdenteufel (2011)	Does not fulfil selection criteria. No control group. Descriptive.
Hash (1999)	Does not fulfil selection criteria. No control group. Descriptive.
Idée JM (2015)	Does not fulfil selection criteria. No control group. Descriptive.
Mikkonen (1995)	Does not fulfil selection criteria. No control group. Descriptive.
Newmark JL (2012)	Does not fulfil selection criteria. No control group. Descriptive.
Rosado Ingelmo (2016)	Does not fulfil selection criteria. No control group. Descriptive.
Scherer K (2010)	Does not fulfil selection criteria. No control group. Descriptive.
Seitz CS (2009)	Does not fulfil selection criteria. No control group. Descriptive.
Stovsky MD (1995)	Does not fulfil selection criteria. No control group. Descriptive.
Webb JAW (2003)	Does not fulfil selection criteria. No control group. Descriptive.

Literature search

Database	Search string	Total
PubMed 1985 – 3th of January 2018	((((((("Contrast Media"[Majr] OR contrast medi* [ti] OR contrast agent* [ti] OR contrast material* [ti] OR contrast dose [ti] OR contrast doses [ti] OR contrast dosage [ti] OR radiocontrast medi* [ti] OR radiocontrast agent* [ti] OR radiopaque medi* [ti] OR radiocontrast dose [ti] OR radiocontrast doses [ti] OR radiocontrast dosage [ti] OR "Barium"[Mesh] OR barium [tiab] OR gadolinium [tiab] OR microbubble* [tiab]))) AND ((("Drug Hypersensitivity"[Mesh] OR hypersensitiv* [tiab] OR allerg* [tiab] OR anaphylax* [tiab] OR anaphylact* [tiab] OR "Exanthema"[Mesh] OR exanthem* [tiab] OR rash [tiab] OR adverse reaction*[tiab] OR urticaria* [tiab] OR erythem* [tiab] OR hypotension [tiab] OR hypertension [tiab] OR "Stevens-Johnson Syndrome"[Mesh] OR stevens johnson syndrome [tiab] OR sjs [tiab] OR toxic epidermal necrolys* [tiab] OR "Drug Hypersensitivity Syndrome"[Mesh] OR dress syndrome [tiab] OR iodide mump* [tiab]) AND (late [tiab] OR delayed [tiab] OR nonimmediate [tiab])) OR late reaction* [tiab] OR delayed reaction* [tiab] OR nonimmediate reaction* [tiab]))) AND (("english"[Language]) AND ("1985"[Date - Publication] : "3000"[Date - Publication]))) = 320	419
Embase (Elsevier)	(('contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage)):ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp/mj OR barium:ab,ti OR 'gadolinium'/exp/mj OR gadolinium:ab,ti OR 'microbubble'/exp/mj OR microbubble*:ab,ti) AND (('hypersensitivity'/exp OR hypersensitiv*:ab,ti OR anaphylax*:ab,ti OR allerg*:ab,ti OR 'rash'/exp OR rash:ab,ti OR 'adverse reaction*':ab,ti OR hypotension:ab,ti OR hypertension:ab,ti OR urticaria*:ab,ti OR erythem*:ab,ti OR exanthem*:ab,ti OR 'stevens johnson syndrome'/exp OR 'stevens johnson syndrome':ab,ti OR sjs:ab,ti OR 'toxic epidermal necrolysis'/exp OR 'toxic epidermal necrolys*':ab,ti OR 'dress syndrome'/exp OR 'dress syndrome':ab,ti OR 'iodide mump*':ab,ti) AND (late:ab,ti OR delayed:ab,ti OR nonimmediate:ab,ti) OR (((late OR delayed OR nonimmediate) NEAR/2 reaction*):ab,ti))) AND [english]/lim AND [1985-2018]/py NOT 'conference abstract':it NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) =370	

3.5 Follow up strategies for hypersensitivity reactions to CM

3.5.1 In vitro tests in patients with hypersensitivity reactions to CM

Validity and maintenance

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

Knowledge gaps

The currently available *in vitro* tests for immediate hypersensitivity reactions (i.e. tryptase measurement and BAT) do not fully differentiate between IgE- and non-IgE-mediated activation. There is a need for better distinction between these reactions, either by optimizing and standardizing thresholds of the currently available tests, or by developing new diagnostic tools that can distinguish between activation via de FcE-receptor or via other receptors. This distinction is clinically relevant as IgE-mediated IHM have a high recurrence risk and re-exposure is contra-indicated, while this usually not the case for non-IgE-mediated reactions.

For nonimmediate hypersensitivity reactions, there are currently no *in vitro* tests available. Particularly for patients with severe NIHM in which *in vivo* testing is contra-indicated or diagnostics cannot be delayed > 6 months, there is an urgent need for *in vitro* diagnostic modalities.

Quality assurance indicators

Not applicable.

Implementation of recommendations

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

Evidence tables

Not applicable

Table of excluded studies

Author and year	Reasons for exclusion
Cabañas, 2018	Does not comply with PICO (Wrong study type, no comparison, wrong population)
Kolenda, 2018	Does not comply with PICO (wrong study type, editorial)
Meucci, 2020	Does not comply with PICO (Wrong intervention, wrong comparison)
Sodagari, 2017	Does not comply with PICO (wrong study type, no comparison, case series, wrong outcome)
Tang, 2020	Does not comply with PICO (Wrong study type, no comparison)
Torres, 2021	Does not comply with PICO (Wrong study type, guideline paper)
Zhai, 2017	Does not comply with PICO (wrong outcome)

Literature search strategy

Search strategy

General information

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

Results

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

Search strategy

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

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

3.5.2 Diagnostic value of skin tests for hypersensitivity reactions after CM

Validity and maintenance

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

Knowledge gaps

Current literature is hampered by its quality, as study set-ups are limited, study populations vary, and a gold standard is generally lacking. Multicentre, structured, and prospective clinical studies are required to establish the value of skin tests for HSRs. For such studies, the clinical features of HSR need to be clearly described and immediate HSR are preferably confirmed by increased tryptase levels. Skin tests should be performed within 12 months after the HSR occurred and the culprit should be known. Analysis should include the culprit contrast agent and a panel of potential alternatives; these materials should become easily accessible for all practicing allergologists.

Availability of affordable diagnostic test kits including various contrast media would greatly facilitate the diagnostic process. Finally, ST findings should be confirmed with re-exposure to (an alternative) contrast agent in real-life or with a DPT.

Quality assurance indicators

Not applicable.

Implementation of recommendations (see also barriers in Supplement)

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

Evidence tables

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

			erythema after 20 min Immediate (IHR): <1 hour after ICM administration Delayed (DHR): >1 hour after ICM administration				

Risk of bias table

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

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
Meucci, 2020	Was a consecutive or random sample of patients enrolled? Unclear No information on how study participants were included/selected Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? No	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Yes	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Not clear if outcome assessors were similar for index and reference tests.	Was there an appropriate interval between index test(s) and reference standard? Unclear Not mentioned in the paper. Did all patients receive a reference standard? Yes Did patients receive the same reference standard? No Patients received same test, but with different contrast media, for provocation. No risk of bias. Were all patients included in the analysis? No	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? Unclear	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? No	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear	CONCLUSION Could the patient flow have introduced bias? Yes	
	RISK: UNCLEAR	RISK: LOW	RISK: UNCLEAR	RISK: HIGH	

Table of excluded studies

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

Literature search strategy

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

3.5.3 Risk factors for hypersensitivity reactions to CM

Validity and maintenance

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

Knowledge gaps

Identifying risk factors for severe HSR such as anaphylaxis and SCAR has the highest clinical relevance. However, these HSR are (fortunately) rare.

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

Quality assurance indicators

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

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

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

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

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

Implementation of recommendations

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

Evidence tables

Evidence table for prognostic studies

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Estimates of prognostic effect	Comments
Cha, 2019	Type of study: prospective cohort Setting and country: South Korea, Between March 2017 and October 2017 Funding and conflicts of interest: All the authors disclosed no relevant relationships.	Inclusion criteria: All patients who underwent contrast-enhanced CT examinations between March 2017 and October 2017. Exclusion criteria: not reported N= 196081 Mean age ± SD: 59.1± 16.0 years Sex: 53.56 % M /46.44 % F Potential confounders or effect modifiers: age, sex, ICM product used, and the institution	Describe prognostic factor(s) and method of measurement: Age, sex, and underlying disease such as diabetes mellitus, heart failure, and hyperthyroidism; previous individual history of ICM usage and ICM-related HSRs; previous individual history of drug allergy, asthma, and other allergic diseases; family history of ICM-related HSRs and allergic diseases, including asthma; name of the administered ICM product; regimen of premedication, if administered; and in instances of HSR occurrence, the symptoms, severity (mild, moderate, and severe), and duration of the HSR, along with details on its management. To assess the risk factors for ICM-related HSRs, a control group was selected among patients without HSRs, after 1:1 matching for age, sex, ICM product used, and the institution. When the occurrence of HSR was reported, control group was selected on a case-by-	Duration or endpoint of follow-up: Not reported For how many participants were no complete outcome data available? Not reported Reasons for incomplete outcome data described? Not reported	(Adjusted) Factor-outcome associations (include SEs or 95%CI and p-value if available): The following factors were associated with increased risk of occurrence and recurrence of ICM related HSRs: Hyperthyroidism (OR: 4.00, 95% CI: 1.4 to 12.1) Drug allergy (OR: 5.2, 95% CI: 2.8 to 9.7) Asthma (OR: 2.3, 95% CI: 1.1 to 4.9) Other allergic disease (OR: 9.5, 95% CI: 4.1 to 22.1) Past history of ICM exposure o HSR to ICM (OR: 56.3, 95% CI: 20 to 151) Family history o HSR to ICM (OR: 11.1, 95% CI: 1.4 to 85.9) The following factor were associated with decreased risk of occurrence and recurrence of ICM related HSRs: Past history of ICM exposure o No HSR to ICM usage (OR: 0.7, 95% CI: 0.6 to 0.8)	

			case basis from the patients of the same age, sex, and institution with the same ICM product administered within 1-week interval from the HSR occurrence. Comparisons between patients with HSR occurrence during the study period and a control group without HSRs were performed. In addition, patients who experienced recurrent HSRs were compared with those who had previously experienced an HSR but had not shown recurrence, to identify the risk factors for its recurrence (Fig 1).		Incremental predictive value[1]: Not reported	
Endrikat, 2020	Type of study: case control Setting and country: Europe, Asia (excluding China), China, Africa Funding and conflicts of interest: Three authors are employees of Bayer; R.K. is a statistician for PAREXEL and paid for his service.	Inclusion criteria: The population were composed of patients who received iopromide 300 or 370 mg I/mL (Ultravist 300/370; Bayer AG, Germany) either IA or IV for contrast-enhanced CT scans for various diagnostic reasons. Exclusion criteria: Patients with unspecific reactions (eg, headache, nausea) and possibly procedure- related reactions (eg, drop in blood pressure, bradycardia, tachycardia) N= 133,331 Mean age ± SD: 50.9 ± 15.72	Describe prognostic factor(s) and method of measurement: The primary target variable was the risk (odds ratio) of having a hypersensitivity reaction after IA versus IV administration of iopromide, adjusted for potential confounders. Secondary target variables pertained to assessing the impact of pretreatment with antihistamines/corticosteroids and to evaluate the profile of reactions within each route of administrations.	Duration or endpoint of follow-up: Not reported For how many participants were no complete outcome data available? N (%):17,763 Reasons for incomplete outcome data described? A total of 17,763 patients had to be excluded from the FAS as key parameters were not sufficiently recorded.	(Adjusted) Factor-outcome associations (include SEs or 95%CI and p-value if available): The following factors were associated with increased risk of HSR: Age 50-<65 (OR: 1.67, 95% CI: 1.38 to 2.02) 18-<50 (OR: 2.16, 95% CI: 1.78 to 2.62) Female (OR: 1.16, 95% CI: 1.01 to 1.34) Diabetes mellitus (OR: 1.54, 95% CI: 1.19 to 2.00) Allergy (OR: 3.61, 95% CI: 2.84 to 4.59) Asthma (OR: 2.14, 95% CI: 1.26 to 3.62)	

		Sex: 56.4 % M / 43.6 % F Potential confounders or effect modifiers: geographic region (China, Asia), age, examination region (abdomen, heart, thorax, pelvis, kidneys), indication (tumour), and type of examination (CT, angiocardiography). No difference was seen for premedication, neither for corticosteroids nor for H1/H2 blocker			Contrast media reaction (OR: 4.31, 95% CI: 2.75 to 6.75) Other concomitant disease: (OR: 1.42, 95% CI: 1.19 to 1.70) Geographic region: Asia (OR: 1.80, 95% CI: 1.54 to 2.11) Dose of iodine in CM o >20–40 g (OR: 1.24, 95% CI: 1.01 to 1.51) Iopromide concentration o Iopromide 370 (OR: 1.31, 95% CI: 1.12 to 1.54) The following factor were associated with increased risk of HSR: IA Injection route (OR: 0.23, 95% CI: 0.16 to 0.32) Incremental predictive value[1]: Not reported	
Kim, 2017	Type of study: Retrospective cohort Setting and country: South Korea, January 2006 and December 2010 Funding and conflicts of interest: This research was supported by a grant from the	Inclusion criteria: Using the spontaneous reporting programme and CDRS, 1969 immediate ADRs from 286 087 examinations of 142 099 patients who performed contrasted CT examinations between January 2006 and December2010 were enrolled in this study, and their medical records were reviewed. Exclusion criteria: Not reported	Describe prognostic factor(s) and method of measurement: Possible risk factors for immediate ADR were also examined. Cases involving the following RCMs were considered (Table 1): iobitridol (Guerbet, Sulzbach, Germany), iohexol (GE healthcare, Amersham, UK), iopamidol (Bracco, Milan, Italy), and iopromide (Schering, Berlin, Germany). Cases were grouped according to the frequency of CT	Duration or endpoint of follow-up: Not reported For how many participants were no complete outcome data available? N (%): Not reported Reasons for incomplete outcome data described? Not reported	(Adjusted) Factor-outcome associations (include SEs or 95%CI and p-value if available): The following factors were associated with increased risk of immediate ADR: •Types of RCMs oIohexol (OR: 1.36, 95% CI:1.08 to 1.72) oIopamidol (OR: 1.59, 95% CI: 1.28 to 1.98) oIopromide (OR: 2.72, 95% CI: 2.17 to 3.41) •Multiple CT (OR: 2.13, 95%	

	Ministry of Food and Drug Safety for the operation of the regional pharmacovigilance centre in 2016.	N= 142 099 Mean age ± SD: 51.60± 18.50 Sex: 50.6 % M / 49.4 % F Potential confounders or effect modifiers: Age, sex, body weight	examinations per day (single CT, multiple CT). Single CT refers to one CT examination per day, while multiple CT refers to more than one CT examination per day. Patient age, gender, and body weight were also considered.		CI: 1.89 to 2.38) •Female (OR: 1.51, 95% CI: 1.36 to 1.67) •Age 20 to 50 (OR: 1.55, 95% CI: 1.01 to 2.37) •Body weight (OR: 1.02, 95% CI: 1.01 to 1.02) The following factors were associated with increased risk of anaphylaxis: •Iopromide (OR: 6.24, 95% CI: 1.32 to 29.44) •Multiple CT (OR: 3.26, 95% CI: 1.81 to 5.86) The following factors were not independently associated with the risk of anaphylaxis: Iohexol, Iopamidol, sex, age and body weight. Incremental predictive value[1]: Not reported	
Park, 2019	Type of study: Retrospective cohort Setting and country: South Korea Funding and conflicts of interest: All the authors disclosed no relevant relationships. This study was funded by Central Medical Service (Seoul, South Korea) and the Korea Health	Inclusion criteria: Patients who had undergone abdominal CT with intravenous contrast material enhancement before (August 2016 to January 2017; control period) or after (August 2017 to January 2018; intervention period) the transition to the lower tube voltage, patients at least 18 years of age, and patients who underwent CT on an outpatient basis. Exclusion criteria: Not reported. N= 48438	Describe prognostic factor(s) and method of measurement: Not described explicitly, but described in results section (see column Outcomes).	Duration or endpoint of follow-up: Not reported For how many participants were no complete outcome data available? N (%): 683 (1.41%) Reasons for incomplete outcome data described? One examination was performed with iodixanol and was excluded from Analysis. Information on patient weight was missing for 682 examinations (1.3%;	(Adjusted) Factor-outcome associations (include SEs or 95%CI and p-value if available): Female (RR:1.22 (95% CI: 1.04 to 1.43) History of acute hypersensitivity to iodinated contrast material (RR: 10.4, 95% CI: 4.51 to 24.2) Contrast material used for study CT o Iomeprol (RR: 4.48, 95% CI: 3.09 to 6.48) Iodine concentration for study CT 350 mg I/mL (RR: 4.66, 95% CI: 2.92 to 7.42)	Statistical analysis regarding identifying the risk factor are not clearly described. Study design is also not suitable for determining the risk factors.

	Technology R&D Project, through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, South Korea	Mean age ± SD: 59 ±12 years Sex: 64.1% M / 35.9 % F Potential confounders or effect modifiers: age, sex, body weight, history of acute hypersensitivity reactions to iodinated contrast material, use of premedication, contrast material and concentration, and type of CT examination		347 and 335 examinations from the control and intervention periods, respectively).	≥370 mg I/mL (RR: 2.83, 95% CI: 2.13 to 3.77) The following factor were associated with decreased risk of acute HSRs: Age (RR: 0.98, 95% CI: 0.97 to 0.98) Premedication for study CT Antihistamine alone (RR: 0.39, 95% CI: 0.17 to 0.9) Steroid with or without antihistamine (RR: 0.37, 95% CI: 0.16 to 0.89) Type of CT examination o Multiphase (RR:0.41, 95% CI: 0.32 to 0.52) Incremental predictive value[1]: Not reported	
Sohn, 2019	Type of study: Prospective observational Setting and country: South Korea, February 2015 to October 2015 Funding and conflicts of interest: The authors state that this work has not received any funding. The authors of this manuscript declare no relationships with	Inclusion criteria: Patients who underwent CAG. Exclusion criteria: not reported N= 714 Mean age ± SD: 62.9 ± 10.3 Sex: 71% M/29% F Potential confounders or effect modifiers: not reported.	Describe prognostic factor(s) and method of measurement: To determine the presence of immediate HSR after CAG, a nurse observed patients in the recovery room for 1 h; for delayed HSR, four nurses affiliated with the Pharmacovigilance Centre conducted phone interviews at 6- to 12-h and 1-, 3-, 7-, and 14-days post-examination to investigate the occurrence of following reactions: cutaneous (rash, urticaria, erythema, pruritus, or heat sensation), cardiovascular system (chest discomfort or palpitations), respiratory system (dyspnea or	Duration or endpoint of follow-up: 2 weeks For how many participants were no complete outcome data available? Not reported Reasons for incomplete outcome data described? Not reported	(Adjusted) Factor-outcome associations (include SEs or 95%CI and p-value if available): Previous IA exposure (+) Unadjusted OR (95% CI): 2.51 (1.08–5.86), p –value: 0.028 Adjusted OR (95% CI): 2.92 (1.22–6.96), p –value: 0.015. Iodixanol Unadjusted OR (95% CI): 1.62 (1.07–2.44), p –value: 0.021 Adjusted OR (95% CI): 1.61 (1.07–2.43), p –value: 0.024. Incremental predictive value[1]: Not reported.	

	any companies whose products or services may be related to the subject matter of the article.		wheezing), digestive system (nausea or vomiting), nervous system (dizziness), urinary system (urinary symptoms), musculoskeletal system (pain), upper airway system (epistaxis), and fever.			

Risk of bias table

Quality assessment for prognostic studies

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

Table of excluded studies

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

Literature search strategy

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

3.5.4 Prophylactic measures to avoid hypersensitivity reactions to CM

Validity and maintenance

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

Knowledge gaps
Not reported.

Quality assurance indicators
See previous module.

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

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

Evidence tables

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Bhatti, 2018	Type of study: retrospective cohort Setting and country: November 1, 2008- January 31, 2016; USA Funding and conflicts of interest: None declared.	Patients with breakthrough reactions to gadobenate dimeglumine Inclusion criteria: Not reported Exclusion criteria: Not reported N total at baseline: Intervention: 19 Control: 97 Important prognostic factors2: Mean age ± SD: I: 51 years (range, 28-90 years) C: Not reported Sex, female: I: 95% (18/19) C: % Not reported Groups comparable at baseline? Not reported	Describe intervention (treatment/procedure/test): 13-hour premedication: 150 mg prednisone (50mg 13, 7, and 1 hour before contrast material) and 50 mg oral diphenhydramine (1 hour before contrast material)	Describe control (treatment/procedure/test): No premedication	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Breakthrough reactions: I: Mild: 8/19 (42%) Moderate: 9/19 (47%) Severe: 2/19 (11%) C: Mild: 65/97 (67%) Moderate: 27/97 (28%) Severe: 5/97 (5%)	

Cha, 2019	Type of study: Retrospective Multicentre registry Setting and country: seven tertiary referral hospitals in Korea Funding and conflicts of interest: No conflicts of interest	Inclusion criteria: all patients who underwent contrast-enhanced CT examinations between March 2017 and October 2017 and who had experienced an HSR to ICM in the past Exclusion criteria: Not reported N total at baseline: Total: 570 Intervention: 213/570 (37.4%) Control: Important prognostic factors: Not reported Groups comparable at baseline? Not reported	Describe intervention (treatment/procedure/test): Mild index reaction, 4 mg of intravenous chlor-pheniramine 30 minutes before ICM administration; Moderate index reaction, 40 mg of intravenous methylprednisolone and 4 mg of intravenous chlorpheniramine 1 hour before ICM administration; Severe index reaction, 40 mg of intravenous methylprednisolone 4 hours and 1 hour before ICM administration and 4 mg of intravenous chlorpheniramine 1 hour before ICM administration via the intravenous cannula inserted for ICM injection	Describe control (treatment/procedure/test): No premedication	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Breakthrough reactions: I: 158/570 (27.7%) C: 19/29 (65.6%) premedication with antihistamine (OR, 0.53; 95% CI: 0.33, 0.86; P = .01)	

Mervak, 2017	Type of study: Retrospective cohort Setting and country: USA Funding and conflicts of interest: No conflict of interest; full report available in the full text article	Inclusion criteria: patients who received accelerated 5-hour IV corticosteroid pro-phylaxis before Contrast material–enhanced CT for a prior allergic-like or unknown-type reaction to iodine-based contrast media Exclusion criteria: (a) no contrast-enhanced CT performed within 24 hours (n = 124), (b) receipt of premedication for 10 hours or longer despite initial documentation indicating that an accelerated regimen was planned (n = 21), (b) premedication performed before an examination other than CT (coronary angiography [n = 17], visceral angiography [n	Describe intervention (treatment/procedure/test): 5-hour IV corticosteroid premedication protocol consisting of 200 mg of IV hydrocortisone administered at 5 hours and 1 hour before CT (total, 400 mg of hydrocortisone administered by means of IV) and 50 mg of IV diphenhydramine administered 1 hour before CT	Describe control (treatment/procedure/test): 50 mg prednisone administered 13 and 7 hours and 1 hour before CT (total, 150 mg prednisone) and 50 mg diphenhydramine administered 1 hour before CT	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Breakthrough reaction rate: I: 5% (5/202; 95% CI: 0.8%, 5.7%) C: 2.1% (13/626, 95% CI: 1.1%, 3.5%) P = .0181 I: Mild: 2/5 (40%) Moderate: 1/5 (20%) Severe: 2/5 (40%)	

		= 11], magnetic resonance im-aging [n = 15], fluoroscopy [n = 3], myelography [n = 1]), (d) subject received oral rather than IV premedication (n = 4), and (e) spurious matching of search terms (n = 1). N total at baseline: Intervention: 202 Control:626 Important prognostic factors2: For example age ± SD: I: 58(11-86) C: 57(5-97) Sex: Male I: 81/202 (40%) C: 229/626 (37 %) Groups comparable at baseline? Yes					

Park, 2017	Type of study: Retrospective multicentre cohort Setting and country: 11 centres, Korea 1 January 2014 - 31 December 2014 Funding and conflicts of interest: The authors state that this work has not received any funding. No conflicts of interest.	Inclusion criteria: Patients who had previously experienced a moderate or severe initial HSR to LOCM and in whom the subsequent exposure occurred Exclusion criteria: Not reported N total at baseline: 150 patients, 328 re- exposure Intervention: 240 Control: 88 Important prognostic factors2: age ± SD: 61.7±11.5 I: Not reported C: Not reported Sex: I: % M C: % M Not reported Groups comparable at baseline? Not reported	Describe intervention (treatment/procedure/test): antihistamines or systemic steroids 0.5–1 hour before re-exposure to LOCM.	Describe control (treatment/procedure/test):	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Recurrence rate of HSR: premedicated with a steroid equivalent to < 40 mg (19.7%; 13/66) or ≥40 mg of prednisolone (26.8%; 15/56) (P = 0.353) steroid premedication: (OR: 1.115, 95% CI: 0.551–2.257; P = 0.762)	

Park, 2018	Type of study: Retrospective cohort Setting and country: Korea January 2012 -December 2015 Funding and conflicts of interest: No conflict of interest	Inclusion criteria: patients who experienced mild HSR to ICM before or during the study period and subsequently underwent contrast material–enhanced CT Exclusion criteria: patients premedicated with systemic steroid (n = 363) were excluded N total at baseline: Intervention: 2388 Control: 1145 *Re-exposures Important prognostic factors2: For example age ± SD: I: C: Not reported Sex: I: % M C: % M Not reported Groups comparable at baseline? Not reported	Describe intervention (treatment/procedure/test): For patients with a mild index reaction, a regimen including 4 mg of intravenous chlorpheniramine 30 minutes before ICM ad- ministration was advised.	Describe control (treatment/procedure/test): No premedication	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	Outcome measures and effect size (include 95%CI and p-value if available): HSR recurrence rate: Premedication with an antihistamine: I: 10.7% C: 16.6% (OR, 0.569; 95% CI: 0.443, 0.731; P, .001) Premedication with the same contrast media: OR, 0.627; 95% CI: 0.430, 0.912; P = .015; with different contrast media: OR, 0.584; 95% CI: 0.4240, 0.776; P, .001	

Ryoo, 2019	Type of study: Retrospective cohort Setting and country: Korea October 2012 - July 2017 Funding and conflicts of interest: The authors report no conflicts of interest.	Inclusion criteria: patients with mild immediate HSR to GBCA who subsequently underwent enhanced magnetic resonance imaging between Exclusion criteria: The patients with unknown culprit agents or unknown adverse reactions were excluded. N total at baseline: 185 patients and 397 re-exposures Intervention: Control: Important prognostic factors2: age ± SD: 51.0 ± 15.2 Sex: 70/185 (37.8%) M Groups comparable at baseline?	Describe intervention (treatment/procedure/test): intravenous administration of chlorpheniramine 4 mg, 30 minutes before GBCA administration for the patients with prior mild HSR, and intravenous administration of methylprednisolone sodium succinate 40 mg plus chlorpheniramine 4 mg, 1 hour before the GBCA administration for the patients with prior moderate or severe HSR.	Describe control (treatment/procedure/test): intravenous administration of chlorpheniramine 4 mg, 30 minutes before GBCA administration for the patients with prior mild HSR, and intravenous administration of methylprednisolone sodium succinate 40 mg plus chlorpheniramine 4 mg, 1 hour before the GBCA administration for the patients with prior moderate or severe HSR.	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	Outcome measures and effect size (include 95%CI and p-value if available): HSR recurrence rate: Premedication I: 20.4% (61/299) C: 17.3% (17/98) OR, 1.221; 95% CI, 0.674–2.211; P = 0.509 antihistamine administration: 19.9%; OR, 1.180; 95% CI, 0.647–2.154; P = 0.589 systemic steroid plus antihistamine: 25.9%; OR, 1.668; 95% CI, 0.609–4.565; P = 0.316	

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

Specjalski, 2020	Type of study: Prospective cohort Setting and country: Poland January 2015-January 2018 Funding and conflicts of interest: Publication of the article financed by ST-554 Gdansk Medical University; The authors declare no conflict of interest	Inclusion criteria: history suggesting a mild hypersensitivity reaction (urticaria, itching, angioedema etc.) Exclusion criteria: Patients with the history of a severe drug hypersensitivity reaction, Including anaphylaxis as defined by Sampson [5], unstable asthma, renal insufficiency or unstable heart insufficiency were excluded from the study. We also excluded patients with isolated subjective vasomotor symptoms (nausea, sweating, feeling of warmth etc.). N total at baseline: Intervention: 40 Control: 36 Important prognostic factors2: Age	Describe intervention (treatment/procedure/test): 10 mg cetirizine + 20 mg prednisone orally 13, 7 and 1 h before the ICM administration.	Describe control (treatment/procedure/test): 10 mg cetirizine + 50 mg prednisone orally 13, 7 and 1 h before the ICM administration.	Length of follow-up: 24 hours Loss-to-follow-up: Total: 24.8 % (25/101) (9/101 patients consent withdrawal; 14/101 patients alternative test chosen (MRI, USG etc.); 1/101 patient withdrawn due to poor compliance; 11/101 patient withdrawn due to unstable condition) Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	Outcome measures and effect size (include 95%CI and p-value if available): hypersensitivity reaction: I: 2/40 (5%) C: 4/36 (11.1%) (p = 0.1306)	

		(range): I: 48.9 (53–82) C: 46.5 (40-90) Sex: I: 21/40 (52.5%) M C: 15/36 (41.7%) M Groups comparable at baseline? Yes					
Walker, 2020	Type of study: Prospective cohort Setting and country: Canada September 2019-September 2020 Funding and conflicts of interest: None declared.	Inclusion criteria: Patients with history of immediate HR or "allergy" to GBCA. Exclusion criteria: Patients who received Gadoterate for reasons other than a previous immediate HR, including physiologic reactions, were excluded N total at baseline: 26 patients, 27 injections Intervention: 19/27 Control:8/27 *Injections Important prognostic	Describe intervention (treatment/procedure/test): 13-hour oral corticosteroid and diphenhydramine premedication	Describe control (treatment/procedure/test): No premedication	Length of follow-up: Not reported Loss-to-follow-up: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported Incomplete outcome data: Intervention: N (%) Reasons (describe) Not reported Control: N (%) Reasons (describe) Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Immediate HRS rate: I: 3.7% (1/27; 95% CI, 0.09%–18.9%) Patients who received adequately dosed corticosteroid premedication: (6.3%; 95% CI, 0.16%–28.7%) Patients who did not receive adequately dosed corticosteroid premedication: (0%, 0/11[upper bound of 95% CI, 25.0%]).	

		factors2: age ± SD: 52.1 ± 15.8 Sex: 84.6%(22/26) F Groups comparable at baseline? Yes					

Risk of bias table

Author, year	Selection of participants Was selection of exposed and non-exposed cohorts drawn from the same population?	Exposure Can we be confident in the assessment of exposure?	Outcome of interest Can we be confident that the outcome of interest was not present at start of study?	Confounding-assessment Can we be confident in the assessment of confounding factors?	Confounding-analysis Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables?	Assessment of outcome Can we be confident in the assessment of outcome?	Follow up Was the follow up of cohorts adequate? In particular, was outcome data complete or imputed?	Co-interventions Were co-interventions similar between groups?	Overall Risk of bias
Bhatti, 2018	Definitely yes Reason: Participants were selected from same population	Probably no Reason: Although data were collected from department adverse incident forms, It is possible that some reactions occurred that were not captured on a form.	Definitely no Reason: selection criteria were used including participants with the outcome of interest at the start date	Definitely no Reason: No matching or adjustment of plausible prognostic variables	Probably no Reason: Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables	Probably no Reason: Uncertain (no description)	Definitely yes Reason: Follow up was enough.	No information Reason:---	High
Cha, 2019	Definitely yes Reason: Participants were selected from a multicentre registry	Probably yes Reason: questionnaire data with ascertainment rules was used.	Definitely no Reason: selection criteria were used including participants with the	Definitely yes Reason: Comprehensive matching or adjustment for all plausible prognostic	Definitely yes Reason: variables were taken into account in the multivariate analysis.	Probably no Reason: Independent assessment unblinded	Definitely yes Reason: Follow up was enough.	No information Reason: ---	Some concern

			outcome of interest at the start date	variables					
Mervak, 2017	Definitely no Reason: Exposed and unexposed presenting to different points of care over a different time frame	Probably yes Reason: Secure record data with ascertainment rules was used.	Definitely no Reason: selection criteria were used including participants with the outcome of interest at the start date	Definitely no Reason: No matching or adjustment of plausible prognostic variables	Probably no Reason: Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables	Probably no Reason: Uncertain (no description)	Definitely yes Reason: Follow up was enough.	No information Reason:---	High
Park, 2018	Definitely yes Reason: Participants were selected from same population	Probably yes Reason: Data collected from Monitoring and Management System with ascertainment rules was used.	Definitely no Reason: selection criteria were used including participants with the outcome of interest at the start date	Definitely no Reason: No matching or adjustment of plausible prognostic variables	Probably no Reason: Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables	Definitely no Reason: Independent assessment unblinded	Definitely yes Reason: Follow up was enough.	No information Reason:---	High
Park, 2017	Definitely yes Reason: Participants were selected from same population	Probably no Reason: Uncertain how exposure information obtained	Definitely no Reason: selection criteria were used including participants with the outcome of interest at the start date	Definitely yes Reason: Comprehensive matching or adjustment for all plausible prognostic variables	Definitely yes Reason: From data base with documentation of accuracy of abstraction of prognostic data	Probably no Reason: Uncertain (no description)	Definitely yes Reason: Follow up was enough.	No information Reason:---	High
Specjals ki, 2020	Definitely yes	Probably no	Definitely yes	Definitely no	Probably no	Probably no	Definitely yes	No information	High

	Reason: Participants were selected from same population	Reason: Uncertain how exposure information obtained	Reason: Patients were randomly assigned to one of the premedication arms and were followed for outcome of interest.	Reason: No matching or adjustment of plausible prognostic variables	Reason: Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables	Reason: Uncertain (no description)	Reason: Follow up was enough.	Reason:---	
Ryoo, 2019	Definitely yes Reason: Exposed and unexposed drawn for same administrative data base of patients presenting at same points of care over the same time frame	Probably yes Reason: Data collected from Monitoring and Management System with ascertainment rules was used.	Definitely no Reason: selection criteria were used including participants with the outcome of interest at the start date	Definitely no Reason: No matching or adjustment of plausible prognostic variables	Probably no Reason: Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables	Probably no Reason: Uncertain (no description)	Definitely yes Reason: Follow up was enough.	No information Reason:---	High
Walker, 2020	Definitely no Reason: Exposed and unexposed presenting to different points of care over a different time frame	Probably yes Reason: questionnaire data with ascertainment rules was used.	Definitely yes Reason: Patients were prospectively identified and were followed for outcome of interest.	Definitely no Reason: No matching or adjustment of plausible prognostic variables	Probably no Reason: Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables	Probably no Reason: Uncertain (no description)	Definitely yes Reason: Follow up was enough.	No information Reason:---	High

Table of excluded studies

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

Literature search strategy

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

3.5.5 Hypersensitivity reactions after non-vascular CM

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4. GBCA

4.1 Risk factors and prevention of NSF

Knowledge Gaps

It is unclear whether ionic macrocyclic GBCAs compared to non-ionic macrocyclic GBCAs in renal insufficiency patients (eGFR <30 ml/min/1.73m2) are associated with different risk of NSF.

It is unclear whether residual kidney function in dialysis patients is effected by the timing of haemodialysis after administration of GBCA.

It is unclear whether timing of dialysis after administration of GBCA affects patient outcomes.

Quality Assurance Indicators

None.

Implementation of Recommendations

Recommendation	Time frame for implementation: <1 year, 1-years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation1	Actions needed for implementation2	Responsible for actions3	Other remarks
Make an individual risk-benefit analysis with the patient's requesting physician and nephrologist to ensure a strict indication for gadolinium-enhanced MRI in patients with eGFR < 30 ml/min/1.73m2	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
For optimal prevention of NSF in patients with eGFR < 30 ml/min/1.73m2 use low-risk (ionic and non-ionic) macrocyclic GBCAs for medical imaging.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
In patients on chronic haemodialysis, GBCA administration	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

may electively be scheduled shortly before the next haemodialysis session to limit the amount of circulating GBCA.							
For prevention of NSF in patients who are already dependent on haemodialysis or peritoneal dialysis, the administration of GBCA does not have to be followed by an immediate haemodialysis session.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.
[2] Actions needed for implementation, but also actions to promote implementations. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.
[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Table of excluded studies part a

After full text review

Author, year	Reason for exclusion
Agarwal 2009	Does not fulfil PICO criteria: no prognostic factors included
Bahrami 2009	Does not fulfil selection criteria: no multivariate analysis (univariate)
Bernstein 2014	Does not fulfil selection criteria: no multivariate analysis (univariate)
Bruce 2016	Does not fulfil selection criteria: no multivariate analysis
Deray 2014	Does not fulfil PICO criteria: no prognostic factors included
Elmholdt 2011	Does not fulfil selection criteria: no multivariate analysis (univariate)
Lauenstein 2015	Does not fulfil PICO criteria: no prognostic factors included
Marckmann 2007	Does not fulfil selection criteria: no multivariate analysis (univariate)
Martin 2010	Does not fulfil selection criteria: no multivariate analysis
Mazhar 2009	Does not fulfil selection criteria: no multivariate analysis (descriptive statistics)
Michaely 2017	Does not fulfil selection criteria: no multivariate analysis (descriptive statistics)
Nacif 2012	Does not fulfil PICO criteria: no prognostic factors included
Othersen 2007	Does not fulfil selection criteria: no multivariate analysis (descriptive statistics)
Rydahl 2008	Does not fulfil selection criteria: no multivariate analysis (descriptive statistics)
Soulez 2015	Does not fulfil selection criteria: no multivariate analysis (descriptive statistics)
Todd 2007	Does not fulfil PICO criteria: no prognostic factors NSF included
Wang 2011	Does not fulfil selection criteria: no multivariate analysis (univariate)
Zhang 2015	Does not fulfil PICO criteria: no prognostic factors included

Literature search strategy part a

Database	Search String	Total
PubMed 2000 – February 2018	(('contrast medium'/exp OR 'contrast medi*':ti,ab OR 'contrast agent*':ti,ab OR 'contrast material*':ti,ab OR 'contrast induced':ti,ab OR 'contrast related':ti,ab OR 'contrast exposure':ti,ab OR 'contrast dosage':ti,ab OR 'contrast dose*':ti,ab OR 'contrast enhanced':ti,ab OR 'contrast administration':ti,ab OR 'gadolinium'/exp OR gadolinium*:ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR	228

	multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadodiamide:ti,ab OR gadopentetat*:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR 'gadofosveset trisodium':ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR 'ultrasound contrast agent*':ti,ab OR 'us contrast agent*':ti,ab OR 'ultrasound contrast medi*':ti,ab OR sonovue:ti,ab OR optison:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR 'barium'/exp OR barium:ti,ab OR micropaque:ti,ab OR 'e z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab) AND ('nephrogenic systemic fibrosis'/exp/mj OR 'nephrogenic systemic fibros*':ti OR nsf:ti OR 'nephrogenic fibrosing dermopath*':ti OR nfd:ti)) AND ([dutch]/lim OR [english]/lim) NOT [conference abstract]/lim AND [2000-2018]/py Filter SR: ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo: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) = 11 Filter RCT: ((random*[tiab] AND (controlled[tiab] OR control[tiab] OR placebo[tiab] OR versus[tiab] OR versus[tiab] OR group[tiab] OR groups[tiab] OR comparison[tiab] OR compared[tiab] OR arm[tiab] OR arms[tiab] OR crossover[tiab] OR cross-over[tiab]) AND (trial[tiab] OR study[tiab])) OR ((single[tiab] OR double[tiab] OR triple[tiab]) AND (masked[tiab] OR blind*[tiab]))) OR ((random*[ot] AND (controlled[ot] OR control[ot] OR placebo[ot] OR versus[ot] OR versus[ot] OR group[ot] OR groups[ot] OR comparison[ot] OR compared[ot] OR arm[ot] OR arms[ot] OR crossover[ot] OR cross-over[ot]) AND (trial[ot] OR study[ot])) OR ((single[ot] OR double[ot] OR triple[ot]) AND (masked[ot] OR blind*[ot]))) = 7 Filter observationele studies: "cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw] = 205 = 211 uniek	
Embase (Elsevier)	(('contrast medium'/exp OR 'contrast medi*':ti,ab OR 'contrast agent*':ti,ab OR 'contrast material*':ti,ab OR 'contrast induced':ti,ab OR 'contrast related':ti,ab OR 'contrast exposure':ti,ab OR 'contrast dosage':ti,ab OR 'contrast dose*':ti,ab OR 'contrast enhanced':ti,ab OR 'contrast administration':ti,ab OR 'gadolinium'/exp OR gadolinium*:ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadodiamide:ti,ab OR gadopentetat*:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR 'gadofosveset trisodium':ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR 'ultrasound contrast agent*':ti,ab OR 'us contrast agent*':ti,ab OR 'ultrasound contrast medi*':ti,ab OR sonovue:ti,ab OR optison:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR 'barium'/exp OR barium:ti,ab OR micropaque:ti,ab OR 'e z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab) AND ('nephrogenic systemic fibrosis'/exp/mj OR 'nephrogenic systemic fibros*':ti OR nsf:ti OR 'nephrogenic fibrosing dermopath*':ti OR nfd:ti)) AND ([dutch]/lim OR [english]/lim) NOT [conference abstract]/lim AND [2000-2018]/py Filter SR: ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo: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) = 11 Filter RCT: ('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 = 23 Filter observationele studies: 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) = 59	

	= 82 uniek	

Table of excluded studies part b

After full text review

Author (year)	Reasons for exclusion
Andrews (2008)	Not original research: comment
Broome (2007)	Does not meet PICO criteria: no intervention/measures
Coletti (2008)	Not original research: comment
Dawson (2008)	Not original research: narrative
Dawson (2008)	Not original research: comment
Gheuens (2014)	Does not meet PICO criteria: no intervention NSF
Kitajima (2012)	No original research: narrative
Knopp (2008)	Does not meet PICO criteria: no intervention/measures
Murashima (2008)	Does not meet PICO criteria: no intervention NSF
Nicolas (2012)	Does not meet PICO criteria: no intervention/measures comparative research
Panesar (2010)	Does not meet PICO criteria: no intervention
Perazella (2008)	Not original research: guideline
Perazella (2009)	Not original research: narrative
Prince (2008)	Does not meet PICO criteria: no intervention/measures
Prince (2009)	Does not meet PICO criteria: no intervention/measures
Rodby (2008)	Not original research: narrative
Saab (2007)	Not original research: comment
Sena (2010)	Does not meet PICO criteria: no intervention NSF
Silberzweig (2009)	Not original research: narrative
Swaminathan (2007)	Not original research: narrative
Thomsen (2007)	Not original research: guideline
Thomsen (2008)	Not original research: narrative
Thomsen (2013)	Not original research: guideline
Tran (2009)	Does not meet PICO criteria: no prevention
Wiginton (2008)	Does not meet PICO criteria: no intervention/measures
Yantasee (2010)	Not original research: narrative
Yee (2017)	Not original research: editorial
Zhang (2015)	Does not meet PICO criteria: no intervention/measures
Zou (2011)	No original research: narrative

Literature search strategy part b

Database	Search String	Total
PubMed 1996 – March 2018	((Gadolinium-based[tiab] OR "Gadolinium"[Mesh] OR gadolinium[tiab] OR magnetic resonance contrast agent*[tiab] OR MR contrast agent*[tiab] OR magnetic resonance contrast media[tiab] OR MR contrast media[tiab] OR MRI contrast agent*[tiab] OR MRI contrast medium[tiab] OR MRI contrast media[tiab] OR GBCA*[tiab] OR Primovist[tiab] OR Eovist[tiab] OR Omniscan[tiab] OR Magnevist[tiab] OR Optimark[tiab] OR Prohance[tiab] OR Multihance[tiab] OR Dotarem[tiab] OR Gadovist[tiab] OR gadodiamide[tiab] OR gadopentetate[tiab] OR gadoversetamide[tiab] OR gadoteridol[tiab] OR gadobenate[tiab] OR gadoterate[tiab] OR gadobutrol[tiab] OR gadoxetic acid[tiab] OR gadoxetate disodium[tiab] OR "Gadolinium DTPA"[Mesh] OR Gd-DTPA[tiab] OR Gd-HP-DO3A[tiab] OR Gd-DTPA-BMA[tiab] OR Gd-DOTA[tiab] OR Gd-DTPA-BMEA[tiab] OR Gd-BOPTA[tiab] OR Gd-BT-DO3A[tiab] OR Gd-EOB-DTPA[tiab] OR meglumine[tiab] OR dimeglumine[tiab] OR ultrasound contrast agent*[tiab] OR US contrast agent*[tiab] OR ultrasound contrast medi*[tiab] OR Sonovue[tiab] OR Optison[tiab] OR perflutren[tiab] OR hexafluoride[tiab] OR "Barium"[Mesh] OR Barium[tiab] OR Micropaque[tiab] OR E-Z-CAT[tiab] OR E Z CAT[tiab] OR Polibar[tiab] OR Barite[tiab] OR Baritop[tiab]) AND ("Nephrogenic Fibrosing Dermopathy"[Mesh] OR Nephrogenic systemic fibros* [tiab] OR NSF [tiab] OR Nephrogenic fibrosing dermopath* [tiab] OR NFD[tiab]) AND (prevent*[tiab] OR "prevention and control" [Subheading]) AND (("1996/01/01"[PDat] : "3000/12/31"[PDat]) AND English[lang])) NOT (animals[mh] NOT humans[mh]) = 109	142

Embase (Elsevier)	(('gadolinium-based':ti,ab OR 'gadolinium'/exp OR gadolinium:ti,ab OR 'magnetic resonance contrast agent*':ti,ab OR 'mr contrast agent*':ti,ab OR 'magnetic resonance contrast media':ti,ab OR 'mr contrast media':ti,ab OR 'mri contrast agent*':ti,ab OR 'mri contrast medium':ti,ab OR 'mri contrast media':ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadodiamide:ti,ab OR gadopentetate:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR 'ultrasound contrast agent*':ti,ab OR 'us contrast agent*':ti,ab OR 'ultrasound contrast medi*':ti,ab OR sonovue:ti,ab OR optison:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR 'barium'/exp OR barium:ti,ab OR micropaque:ti,ab OR 'e z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab) AND ('nephrogenic systemic fibrosis'/exp OR 'nephrogenic systemic fibros*':ti,ab OR nsf:ti,ab OR 'nephrogenic fibrosing dermopath*':ti,ab OR nfd:ti,ab) AND (prevent*:ti,ab OR 'prevention and control'/exp)) AND [english]/lim AND [1996-2018]/py NOT 'conference abstract':it NOT ([animals]/lim NOT [humans]/lim) = 84	

Evidence tables

-

4.2 Gadolinium deposition

4.2.1 Introduction to gadolinium deposition

-

4.2.2 Gadolinium deposition in the brain and body

Validity and maintenance

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

Knowledge gaps

Not reported.

Quality assurance indicators

Not applicable.

Implementation of recommendations

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

Evidence tables

Not applicable

Table of excluded studies

Not applicable

Literature search strategy

Not applicable

4.2.3 Strategies for dose reduction of GBCA

Validity and maintenance

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

Knowledge gaps

Not reported.

Quality assurance indicators

Not applicable.

Implementation of recommendations

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

Evidence tables

Not applicable

Table of excluded studies

Not applicable

Literature search strategy

Not applicable

4.2.4 GBCA and T1w hyperintensity in the brain

Knowledge gaps

It is not clear what the clinical relevance is of gadolinium-based contrast agent (GBCA) induced T_1w hyperintensity of the nucleus dentatus and the globus pallidus in the brain?

Indicators

None.

Implementation

Recommendation	Time frame for implementation: <1 year, 1 to 3 years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
Ensure a strict indication for gadolinium-enhanced MRI and use EMA-approved GBCA in all patients to minimize possible gadolinium deposition.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.

[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.

[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Table of excluded studies

Table of Excluded studies after reading full text

Author and year	Reason for exclusion
Abraham, 2008	Does not meet selection criteria.
Aruyani 2018	Does not meet selection criteria.
Adin, 2018	Does not meet selection criteria.
Arsenault, 1996	Does not meet selection criteria.
Bae, 2017	Does not meet selection criteria.
Behzadi, 2018	Does not meet selection criteria.
Bhargava, 2018	Does not meet selection criteria.
Bjornerund, 2017	Does not meet selection criteria.
Bolles, 2018	Does not meet selection criteria.
Boyken, 2018	Does not meet selection criteria.
Cao, 2016	Does not meet selection criteria.
Cao, 2016_1	Does not meet selection criteria.
Conte, 2017	Does not meet selection criteria.
Costa, 2018	Not an original article.
Costa, 2018_1	Does not meet selection criteria.
DiGregorio 2018	Does not meet selection criteria.

Errante, 2014	Does not meet selection criteria.
Fingerhut, 2018	Does not meet selection criteria.
Fingerhut, 2018_1	Does not meet selection criteria.
Flood 2017	Does not meet selection criteria.
Frenzel, 2017	Does not meet selection criteria
Frettelier, 2018	Does not meet selection criteria.
Guo, 2018	Does not meet selection criteria.
Hinoda, 2017	Does not meet selection criteria.
Hu, 2016	Does not meet selection criteria.
Huckle, 2016	Not an original article, narrative review.
Ichiwana, 2017	Does not meet selection criteria.
Idee, 2018	Does not meet selection criteria.
Idee, 2018_1	Does not meet selection criteria.
Jaulant, 2018	Does not meet selection criteria.
Jost, 2016	Does not meet selection criteria.
Kahn, 2017	Does not meet selection criteria.
Kanda, 2014	Does not meet selection criteria.
Kanda, 2015	Does not meet selection criteria.
Kang, 2018	Does not meet selection criteria.
Kang, 2018_1	Does not meet selection criteria.
Kasper, 2018	Does not meet selection criteria.
Khant, 2017	Does not meet selection criteria.
Kim, 2018	Does not meet selection criteria.
Kinner, 2018	Does not meet selection criteria.
Kralik, 2018	Does not meet selection criteria.
Kromrey, 2017	Does not meet selection criteria.
Kuno, 2017	Does not meet selection criteria.
Langer, 2017	Does not meet selection criteria.
Lee 2017	Does not meet selection criteria.
Lohrke, 2017	Does not meet selection criteria.
Lord, 2018	Does not meet selection criteria.
Malhotra, 2018	Does not meet selection criteria.
Maria, 2018	Does not meet selection criteria.
McDonald, 2018	Does not meet selection criteria.
McDonald, 2017	Does not meet selection criteria.
McDonald, 2017	Does not meet selection criteria.
Moser, 2018	Does not meet selection criteria.
Murata, 2016	Does not meet selection criteria.
Olchowy, 2017	Does not meet selection criteria, no comparative studies included in review.
Ozturk, 2018	Does not meet selection criteria.
Pasquini, 2018	Does not meet selection criteria.
Perrotta, 2017	Does not meet selection criteria.
Pinter, 2016	Does not meet selection criteria
Pulcino, 2018	Does not meet selection criteria.
Quattrocchi, 2018	Does not meet selection criteria.
Quattrocchi, 2015	Does not meet selection criteria.
Radbruch, 2018	Does not meet selection criteria.
Radbruch, 2017	Does not meet selection criteria.
Radbruch 2017_1	Does not meet selection criteria.
Radbruch, 2015	Does not meet selection criteria.
Radbruch, 2015	Does not meet selection criteria.
Ramalho, 2017	Does not meet selection criteria.
Ramalho, 2016	Does not meet selection criteria.
Ramalho, 2016_1	Does not meet selection criteria.
Ramalho 2016_2	Does not meet selection criteria.
Ramalho, 2015	Does not meet selection criteria.
Rasschaert, 2018	Does not meet selection criteria.
Raynaldo, 2018	Does not meet selection criteria.
Renz, 2018	Does not meet selection criteria.
Roberts, 2017	Does not meet selection criteria.
Roberts, 2017_1	Does not meet selection criteria.

Rossi, 2017	Does not meet selection criteria.
Runge 2017	Does not meet selection criteria.
Ryo, 2018	Does not meet selection criteria.
Schlemm, 2017	Does not meet selection criteria.
Schneider, 2016	Does not meet selection criteria
Splendiani, 2018	Does not meet selection criteria.
Swaminathan, 2016	Does not meet selection criteria.
Tamrazi, 2018	Does not meet selection criteria.
Tamrazi, 2018_1	Does not meet selection criteria.
Taoka, 2018	Does not meet selection criteria.
Taoka, 2018_1	Does not meet selection criteria..
Tedeschi, 2018	Does not meet selection criteria.
Tedeschi 2018_1	Does not meet selection criteria.
Thomsen, 2016	Does not meet selection criteria.
Tibussek, 2017	Does not meet selection criteria.
Weberling, 2015	Does not meet selection criteria.
Xia, 2014	Does not meet selection criteria.
Yoo, 2018	Does not meet selection criteria.
Young, 2017	Does not meet selection criteria.
Young, 2018	Does not meet selection criteria, patient population consists of children.
Young, 2018_1	Does not meet selection criteria.
Zhang, 2017	Does not meet selection criteria.

Literature search strategy

Database	Search string	Total
PubMed 1996 – November 2018	((Gadolinium-based[ti] OR "Gadolinium"[Majr] OR gadolinium[ti] OR magnetic resonance contrast agent*[ti] OR MR contrast agent*[ti] OR magnetic resonance contrast media[ti] OR MR contrast media[ti] OR MRI contrast agent*[ti] OR MRI contrast medium[ti] OR MRI contrast media[ti] OR GBCA*[ti] OR Primovist[ti] OR Eovist[ti] OR Omniscan[ti] OR Magnevist[ti] OR Optimark[ti] OR Prohance[ti] OR Multihance[ti] OR Dotarem[ti] OR Gadovist[ti] OR gadodiamide[ti] OR gadopentetate[ti] OR gadoversetamide[ti] OR gadoteridol[ti] OR gadobenate[ti] OR gadoterate[ti] OR gadobutrol[ti] OR gadoxetic acid[ti] OR gadoxetate disodium[ti] OR "Gadolinium DTPA"[Majr] OR Gd-DTPA[ti] OR Gd-HP-DO3A[ti] OR Gd-DTPA-BMA[ti] OR Gd-DOTA[ti] OR Gd-DTPA-BMEA[ti] OR Gd-BOPTA[ti] OR Gd-BT-DO3A[ti] OR Gd-EOB-DTPA[ti] OR meglumine[ti] OR dimeglumine[ti] OR ultrasound contrast agent*[ti] OR US contrast agent*[ti] OR ultrasound contrast medi*[ti] OR Sonovue[ti] OR Optison[ti] OR perflutren[ti] OR hexafluoride[ti] OR "Barium"[Mesh] OR Barium[ti] OR Micropaque[ti] OR E-Z-CAT[ti] OR E Z CAT[ti] OR Polibar[ti] OR Barite[ti] OR Baritop[ti]) AND ("Basal Ganglia"[Majr] OR "Cerebellar Nuclei"[Majr] OR "Globus Pallidus"[Majr] OR "Brain"[Majr] OR "Tissues"[Majr] OR "Liver"[Majr] OR "Bone and Bones"[Majr] OR "Parkinson Disease"[Majr] OR basal gangli*[ti] OR dentate nucleus[ti] OR globus pallidus[ti] OR brain[ti] OR intracranial[ti] OR bone[ti] OR liver[ti] OR tissue*[ti] OR renal[ti] OR parkinson*[ti]) AND (accumulate*[tiab] OR deposition*[tiab] OR signal intensit*[tiab] OR signal increase*[tiab] OR hyperintensity[tiab] OR hypersignal*[tiab] OR toxicit*[tiab] OR exposure[tiab]) AND (("1996/01/01"[PDat] : "3000/12/31"[PDat]) AND English[lang])) NOT (animals[mh] NOT humans[mh]) = 560 Systematic Reviews: ((review[tiab] OR "Review"[Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR meta-analysis[tiab] OR "Meta-Analysis "[Publication Type]) NOT ("Letter"[Publication Type] OR "Editorial"[Publication Type] OR "Comment"[Publication Type])) NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) 96 Randomized Controlled Trials: randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]	722 (360 SR's, RCT's en Observationele studies + 362 overige studies)

	80 Observationele studies: "cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw] 312 Overige studies: 152	
Embase (Elsevier)	('gadolinium-based':ti OR 'gadolinium'/exp/mj OR gadolinium*:ti OR 'magnetic resonance contrast agent*':ti OR 'mr contrast agent*':ti OR 'magnetic resonance contrast media':ti OR 'mr contrast media':ti OR 'mri contrast agent*':ti OR 'mri contrast medium':ti OR 'mri contrast media':ti OR gbca*:ti OR primovist:ti OR eovist:ti OR omniscan:ti OR magnevist:ti OR optimark:ti OR prohance:ti OR multihance:ti OR dotarem:ti OR gadovist:ti OR gadodiamide:ti OR gadopentetate:ti OR gadoversetamide:ti OR gadoteridol:ti OR gadobenate:ti OR gadoterate:ti OR gadobutrol:ti OR 'gadoxetic acid':ti OR 'gadoxetate disodium':ti OR 'gd dtpa':ti OR 'gd hp do3a':ti OR 'gd dtpa bma':ti OR 'gd dota':ti OR 'gd dtpa bmea':ti OR 'gd bopta':ti OR 'gd bt do3a':ti OR 'gd eob dtpa':ti OR meglumine:ti OR dimeglumine:ti OR 'ultrasound contrast agent*':ti OR 'us contrast agent*':ti OR 'ultrasound contrast medi*':ti OR sonovue:ti OR optison:ti OR perflutren:ti OR hexafluoride:ti OR 'barium'/exp/mj OR barium:ti OR micropaque:ti OR 'e z cat':ti OR polibar:ti OR barite:ti OR baritop:ti) AND ('basal ganglion'/exp/mj OR 'basal gangli*':ti OR 'dentate nucleus'/exp/mj OR 'dentate nucleus':ti OR 'globus pallidus'/exp/mj OR 'globus pallidus':ti OR 'brain'/exp/mj OR brain:ti OR intracranial:ti OR bone:ti OR liver:ti OR tissue*:ti OR renal:ti OR parkinson*:ti OR 'tissues'/exp/mj OR 'liver'/exp/mj OR 'bone'/exp/mj OR 'parkinson disease'/exp/mj) AND (accumulate*:ti,ab OR deposition*:ti,ab OR 'signal intensit*':ti,ab OR 'signal increase*':ti,ab OR hyperintensity:ti,ab OR hypersignal*:ti,ab OR toxicit*:ti,ab OR exposure:ti,ab) AND [english]/lim AND [1996-2018]/py NOT 'conference abstract':it = 535 Systematic Reviews: ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo: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) 4 Randomized Controlled Trials: ('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 81 Observationele studies: 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) 133	

	Overige studies: 317	

5. Pregnancy and lactation

5.1 Safe use of CM during pregnancy

Validity and maintenance

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

Knowledge gaps

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

Quality assurance indicators

Not applicable.

Implementation of recommendations

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

Evidence tables

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Han, 2011	Type of study: observational retrospective Setting and country: Korea Funding and conflicts of interest: none reported The authors report no conflicts of interest. Th e authors alone are responsible for the content and writing of the paper	Inclusion criteria: women who were inadvertently exposed to barium-contrasted X- ray of the upper gastrointestinal tract (UGT), i.e. barium swallow, in early pregnancy Exclusion criteria: none reported N total at baseline: Intervention: 32 Control: 94 Important prognostic factors[2]: *For example age ± SD:* *I: 31.3 ± 3.5* *C: 31.9 ± 4.1* *Medications *number): I: 4.1 ± 4.8* *C: 6.2 ± 4.8* Groups	Describe intervention (treatment/procedure/test): Women who were inadvertently exposed to barium-contrasted X-ray of the upper gastrointestinal tract (UGT), i.e. barium swallow, in early pregnancy Between the 18th and 20th weeks ' gestation, patients underwent physical and high-resolution obstetric ultrasound examinations. Th is high-resolution ultrasound examination was intended to assess proper foetal growth and development, especially to rule out gross malformations, as well as to evaluate the proper location and development of the placenta, and follow- up scans were performed if abnormalities were suspected. Blood samples were collected for routine haematological and biochemical tests, and for the triple screening (α - fetoprotein, human chorionic gonadotropin and unconjugated oestriol levels). At the next prenatal visit, patients were provided with the results of the blood tests and ultrasound examination	Describe control (treatment/procedure/test): For each case included in the study, three age- and gravidity matched consenting controls were identified from a large group of pregnant women who were not exposed to any radio-contrast media or any known or potential human teratogen. At birth, all babies were reviewed by a neonatologist who carefully examined the babies in order to rule out any major or minor gross malformation, neurofunctional abnormalities, or any other possible physiological alteration.	Length of follow-up: unclear, at least until birth so 9 months Loss-to-follow-up: Intervention: N (%) = 10/42 (24%) Spontaneous abortions (n = 1); Voluntary terminations (n = 3); Ongoing pregnancies (n = 2); Lost to follow-up (n = 4) Control: N (%) = 32/126 (25%) Spontaneous abortions (n = 7); Voluntary terminations (n = 6); Ongoing pregnancies (n = 8); Lost to follow- up (n = 11) Incomplete outcome data: see above	Outcome measures and effect size (include 95%CI and p-value if available): There were 32 live- born babies in the exposed group and 94 in the controls. Foetal outcomes among inadvertently exposed women were similar to those observed in the control group (Table II); there was one baby (3.1%) born with a major malformation (left ectopic kidney) in the exposed group and three (3.2%) in the control group (p 1.0). Major congenital malformations in the control group included a baby born with left inguinal hernia; a baby born with meningomyeloceles and a baby born with polydactyly on both hands. One baby was born with minor birth defects in the exposed group (nuchal fold thickness), while in the control group there was a case of gum cyst and another baby born with internal rotation of right foot.	Only patients who had barium exposure in first trimester are included in this study.

		comparable at baseline? Yes	and were counselled accordingly. At birth, all babies were reviewed by a neonatologist who carefully examined the babies in order to rule out any major or minor gross malformation, neurofunctional abnormalities, or any other possible physiological alteration.				
Rajaram, 2012	Type of study: observational retrospective Setting and country: United Kingdom Funding and conflicts of interest: not reported, unlikely to be present considering subject and type of study	Inclusion criteria: all pregnant females investigated for suspected pulmonary embolism who were admitted to study hospitals from April 2004 to April 2009. Exclusion criteria: none reported N total at baseline: Intervention: 73 Control: 42 Important prognostic factors[2]: *For example age (range): I: 32 (21-46)* *C: 30 (17-40)*	Describe intervention (treatment/procedure/test): pregnant patients with suspected pulmonary embolism who had CTPA, and hence received intravenous iodinated contrast media A maximum dose of 100 ml of nonionic iodinated low-molecular-weight agent containing 300 mg I ml–1 Ultravist 300 (Schering AG, Berlin, Germany) was used as a standard contrast agent.	Describe control (treatment/procedure/test): pregnant patients with suspected pulmonary embolism who had perfusion imaging only and did not receive contrast	Length of follow-up: unclear, at least several weeks after birth, so 9 months Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): The average TSH value for group A, exposure to iodinated contrast agent, was 1.1 mIU ml^{-1}. The average TSH value for group B, no exposure to iodinated contrast agent, was 1.07 mIU ml^{-1}. (p=0.67)	

		Gestational age (range): I: 28 (12-40) *C: 29 (7-38)* Groups comparable at baseline? Yes					

Risk of bias table

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

Table of excluded studies

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

Literature search strategy

Search strategy
General information

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

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

Results

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

Search strategy

Database	Search terms		
Embase			
	No.	Query	Results
	#11	#8 OR #9 OR #10	372
	#10	#4 AND #7 NOT (#8 OR #9) - Observational studies	181
	#9	#4 AND #6 NOT #8 - RCTs	135
	#8	#4 AND #5 - SRs	56
	#7	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR cohort*:ab,ti OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	5842012
	#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3202960
	#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR	699308

	database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab #4 #1 AND (#2 OR #3) AND ([english]/lim OR [dutch]/lim) AND [2000-2020]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) 2820 #3 'lactation'/exp OR 'breast feeding'/exp OR 'puerperium'/exp OR lactation:ti,ab,kw OR lactating:ti,ab,kw OR 'breast feeding':ti,ab,kw OR puerperium:ti,ab 187830 #2 'pregnancy'/exp/mj OR pregnant:ti,ab,kw OR pregnancy:ti,ab,kw 705080 #1 'contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage OR induced OR enhanced OR exposure OR administration OR iodinated OR iodine*)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti OR 'gadolinium- based':ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadavist:ti,ab OR gadodiamide:ti,ab OR gadopentetate:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR sonovue:ti,ab OR optison:ti,ab OR lumason:ti,ab OR definity:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR micropaque:ti,ab OR 'e-z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab OR visipaque:ti,ab OR hexabrix:ti,ab OR iomeron:ti,ab OR iopamiro:ti,ab OR omnipaque:ti,ab OR optiray:ti,ab OR ultravist:ti,ab OR xenetix:ti,ab OR iodixanol:ti,ab OR ioxaglate:ti,ab OR iomeprol:ti,ab OR iopamidol:ti,ab OR iosimenol:ti,ab OR iohexol:ti,ab OR ioversol:ti,ab OR iopromide:ti,ab OR iobitridol:ti,ab 281802
Medline (OVID)	1 exp *Contrast Media/ or Barium/ or exp Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium-based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol).ti,ab,kf. (188721) 2 exp Pregnancy/ or pregnant.ti,ab,kf. or pregnancy.ti,ab,kf. (1019925) 3 exp Lactation/ or exp Breast Feeding/ or (lactation or lactating or 'breast feeding' or puerperium).ti,ab,kf. (110401) 4 2 or 3 (1076220) 5 1 and 4 (2275) 6 limit 5 to ((english or dutch) and yr="2000 -Current") (1384) 7 6 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (962) 8 meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or

	((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf. (502787) 9 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2084579) 10 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (3641005) 11 7 and 8 (45) - SRs 12 (7 and 9) not 8 (90) - RCTs 13 (7 and 10) not (8 or 9) (225) – Observational studies 14 11 or 12 or 13 (360)

5.2 Safe use of CM during lactation

Validity and maintenance

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

Knowledge gaps

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

Quality assurance indicators

Not applicable.

Implementation of recommendations

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

Evidence tables

Not applicable.

Table of excluded studies

See chapter 2.

Literature search strategy

See chapter 2.

6. Rare diseases

6.1 Safe use of contrast media in patients with Multiple Myeloma

Validity and maintenance

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

Knowledge gaps

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

Quality assurance indicators

Not applicable.

Implementation of recommendations

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

Evidence tables

Not applicable

Table of excluded studies

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

Literature search strategy

Search strategy

General information

Guideline: Contrast media part 3	
Research question: What is a safe strategy for use of contrast media in multiple myeloma patients?	
Database(s): Medline (OVID), Embase	Date: 17-02-2021
Search from: >2000	Language: English, Dutch
Literature specialist: Linda Niesink	

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

Results

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

Search strategy

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

	#2 'multiple myeloma'/exp OR ((kahler NEAR/2 (disease* OR morbus)):ti,ab,kw) OR ((myeloma NEAR/2 (multiplex OR multiple OR 'plasma cell')):ti,ab,kw) OR myelomatosis:ti,ab,kw 91574 #3 #1 AND #2 AND ([english]/lim OR [dutch]/lim) AND [2000-2020]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) 271 #4 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab 91574 #5 'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti 3202960 #6 'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR cohort*:ab,ti OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) 5842012 #7 #3 AND #4 - SRs 10 #8 #3 AND #5 NOT #7 - RCTs 43 #9 #3 AND #6 NOT (#7 OR #8) – observational studies 51 #10 #7 OR #8 OR #9 104
Medline (OVID)	1 exp *Contrast Media/ or Barium/ or exp Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium- based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol).ti,ab,kf. (189258) exp Multiple Myeloma/ or 'multiple myeloma'.ti,ab,kf. or (kahler adj2 (disease* or morbus)).ti,ab,kf. or (myeloma adj2 (multiplex or multiple or 'plasma cell')).ti,ab,kf. or myelomatosis.ti,ab,kf. (54206) 1 and 2 (274) limit 3 to ((english or dutch) and yr="2000 -Current") (159) 4 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (153) (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (480877) (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2087471)

	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (3656858) 5 and 6 (3) – SRs (5 and 7) not 9 (14) - RCTs (5 and 8) not (9 or 10) – observational studies 9 or 10 or 11 (65)

6.2 Safe use of contrast media in patients with Pheochromocytoma or Paraganglioma

Validity and maintenance

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

Knowledge gaps

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

Quality assurance indicators

Not applicable.

Implementation of recommendations

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

Evidence tables

Not applicable

Table of excluded studies

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

Literature search strategy

Search strategy General information

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

Results

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

Search strategy

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

		'e-z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab OR visipaque:ti,ab OR hexabrix:ti,ab OR iomeron:ti,ab OR iopamiro:ti,ab OR omnipaque:ti,ab OR optiray:ti,ab OR ultravist:ti,ab OR xenetix:ti,ab OR iodixanol:ti,ab OR ioxaglate:ti,ab OR iomeprol:ti,ab OR iopamidol:ti,ab OR iosimenol:ti,ab OR iohexol:ti,ab OR ioversol:ti,ab OR iopromide:ti,ab OR iobitridol:ti,ab	
	#2	'pheochromocytoma'/exp OR 'paraganglioma'/exp OR pheochromocytom*:ti,ab,kw OR pheochromoblastom*:ti,ab,kw OR phaeochromocytom*:ti,ab,kw OR phaeochromoblastom*:ti,ab,kw OR pheochromocytos*:ti,ab,kw OR paraganglio*:ti,ab,kw	41640
	#3	#1 AND #2 AND ([english]/lim OR [dutch]/lim) AND [2000-2020]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	384
	#4	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR ((((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	699308
	#5	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3202960
	#6	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR cohort*:ab,ti OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	5842012
	#7	#3 AND #4 - SRs	11
	#8	#3 AND #5 NOT #7 - RCTs	24
	#9	#3 AND #6 NOT (#7 OR #8) – observational studies	69
	#10	#7 OR #8 OR #9	104
Medline (OVID)	1	exp *Contrast Media/ or Barium/ or exp Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium-based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or	

	gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol).ti,ab,kf. (188788) exp Pheochromocytoma/ or exp Paraganglioma/ or (pheochromocytom* or pheochromoblastom* or phaeochromocytom* or phaeochromoblastom* or pheochromocytos* or paraganglio*).ti,ab,kf. (31853) 1 and 2 (436) limit 3 to ((english or dutch) and yr="2000 -Current") (224) 4 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (203) (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (480877) (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2087471) Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (3656858) 5 and 6 (8) – SRs (5 and 7) not 9 (11) - RCTs (5 and 8) not (9 or 10) (76) – observational studies 9 or 10 or 11 (76)

6.3 Safe use of contrast media in patients with Myasthenia Gravis

Validity and maintenance

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

Knowledge gaps

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

Quality assurance indicators

Not applicable.

Implementation of recommendations

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

Evidence tables

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Somashekar , 2013	Type of study: retrospective cohort Setting and Country*: single large academic health system; January 1, 1995, and December 31, 2011. Michigan, USA Source of funding and conflicts of interest: D.K.S. No relevant conflicts of interest to disclose. M.S.D. No relevant conflicts of interest to disclose. R.H.C. Financial activities related to the present article: none to disclose. Financial activities not related to the present article: is a paid consultant for GE Healthcare; received payment for expert testimony from GE Healthcare, LeClair	Inclusion criteria: pediatric and adult patients with myasthenia gravis who underwent computed tomography (CT) (regardless of indication or body part) Exclusion criteria: neonatal and/or congenital-type myasthenia gravis and if there was conflicting and/or inadequate documentation confirming the presence or absence of contrast material administration. Important patient characteristics at baseline: No of patients: N=267 I: 112 C:155 Male sex: (%) I: 57 (51) C: 76 (49)	Describe intervention: Variety of low- osmolality contrast media Contrast medium type: N (%) Unknown: 54 (48) Iopamidol 300: 32 (29) Iopamidol 370: 11 (10) Iopromide 300: 11 (10) Iohexol 300: 4 (4)	Describe control: Unenhanced CT group	Length of follow-up: 45 days after CT Loss-to-follow-up: Intervention: no loss to follow up because of retrospective study design. Incomplete outcome data: Intervention: no incomplete outcome data because of retrospective study design.	Frequency of acute (≤1 day) disease-related symptoms: I: 6.3% [7/112; 95% CI: 0.03- 0.12] C: 0.6% [1/155; 95% CI: 0.0002-0.04]). P = 0.01 Median time to symptom progression: I: 2.5 days C: 14.0 days P = 0.05 Estimated risk of acute symptom deterioration: 5%–6% above baseline (95% CI: 0%-12%). No difference in symptoms between groups at 2–7 days (P =.70) or 8–45 days (P = .99) contrast material dose and type was unknown in a large minority of patients Adverse Events: Symptom exacerbation within 45 days after CT: I: 7/10 C: 0 Symptom exacerbation occurred within 1 day of CT: I: 4/7 C: 0	primary end point: exacerbation of myasthenia gravis– related symptoms Study limitations: "It was retrospective and there was selection bias between the control group and the experimental group. Some adverse events may not have been captured. we were unable to determine the volume or type of contrast material administered in a large fraction of patients owing to incomplete documentation" Author's conclusion: "In conclusion, we demonstrated a significant association between intravenous low-osmolality contrast material and acute myasthenia gravis symptom exacerbation, with an incremental frequency that is 5%–6% above the baseline rate observed in similar patients undergoing unenhanced CT. This suggests a need for caution in administering low-osmolality contrast material

	Ryan, and John Hickey; receives royalties from Lippincott, Williams, and Wilkins. Other relationships: none to disclose. J.R.D. Financial activities related to the present article: none to disclose. Financial activities not related to the present article: institution has grants/grants pending from GE Healthcare, Bracco Imaging; and Siemens Medical Solutions. Other relationships: none to disclose. J.H.E. Financial activities related to the present article: none to disclose. Financial activities not related to the present article: is a paid consultant for GE Healthcare; received payment for expert testimony from law firm representing GE Healthcare. Other relationships: none to disclose.	Mean age at CT (y): I: 55 (20) C: 58 (21) Groups comparable at baseline: No significant difference between Intervention and control group, except for "Indication for CT"					to patients with myasthenia gravis, and such patients should not place themselves too far from an acute care hospital for a day or two after contrast-enhanced CT in the event that serious symptoms occur."

Rath, 2017	Type of study: retrospective cohort study Setting and country: Department of Neurology of the Medical University of Vienna; between 2005 and 2015 Vienna, Austria Funding and conflicts of interest: Open access funding provided by Medical University of Vienna. This study received no specific grant from any funding agency. None of the authors has any conflict of interest to disclose.	Inclusion criteria: typical clinical symptoms in combination with either a positive test for myasthenia gravis-specific autoantibodies [acetylcholine receptor or muscle-specific kinase (MuSK)], a typical decrement ([10%) shown by repetitive nerve stimulation or a positive edrophonium chloride test Exclusion criteria: congenital myasthenia gravis, concomitant serious renal disease, and an age of less than 18 years. Important patient characteristics at baseline: No of patients: N=125 I: 73 C:52 Male sex: (%) I: 31 (42.5)	Describe intervention: Low osmolality iodinated contrast agents (ICAs)	Describe control: Unenhanced CT	Length of follow-up: 30 days Loss-to-follow-up: Intervention: no loss to follow up because of retrospective study design. Incomplete outcome data: Intervention: no incomplete outcome data because of retrospective study design.	Primary endpoint: I: 9 (12.3%); 95% CI 5.8-22.1% C: 2 (3.8%); 95% CI 0.5-13.2% P = 0.12 (OR 3.52, 95% CI 0.73–17.0) Subtypes of endpoint: Severe (death or myasthenic crisis): I: 6 (8.2%) (4 myasthenic crisis, 2 deaths) C: 0 P value = 0.04 ≥1 increase in MGFA class but not myasthenic crisis or death): I: 3 (4.1%) C: 2 (3.8%) P value = 1.00 Time to primary endpoint: I:11.1 days (SD 8.6) C:13 days (SD 1.4) P value = 0.10 only a single patient (1.4%) with an acute, transient probably anaphylactic reaction (dyspnea) occurring immediately after application of the contrast agent.	Primary endpoint: Clinically relevant deterioration of myasthenic symptoms within 30 days of the CT study, defined as clinical worsening by at least one MGFA class. Secondary endpoints: (a) the occurrence of an immediate, acute adverse reaction as documented in the radiological report (b) in the case of reaching the primary endpoint the time (in days) to clinical deterioration after ICA administration. Study limitations: “Selection bias for the enhanced and unenhanced CT scans and the relatively low patient numbers. The retrospective nature of this investigation entails the possibility that some adverse events might have been missed in some patients as we had to rely on electronic medical records. To minimize this effect, we only included patients with a sufficient clinical information available.” Author’s conclusion: “We conclude that an acute, non-MG-related adverse reaction is a rare event with a risk

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

Risk of bias table

Study reference	Bias due to a non-representative or ill-defined sample of patients? (unlikely/likely/unclear)	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups? (unlikely/likely/unclear)	Bias due to ill-defined or inadequately measured outcome? (unlikely/likely/unclear)	Bias due to inadequate adjustment for all important prognostic factors? (unlikely/likely/unclear)
Rath, 2017	Unclear – because only patients with available sufficient data were included, this leads to selection bias, since there is often a reason that some patients files are better documented than others	Unlikely	Unlikely: the outcome was clearly defined and measured.	Unlikely: the outcome was compared to a well-defined control group.
Somashekar, 2013	Unlikely: only patients with Myasthenia gravis, with confirmed symptoms, were included.	Unlikely	Unlikely: the outcome was clearly defined and measured.	Unlikely: the outcome was compared to a well-defined control group.

Table of excluded studies

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

Literature search strategy

Search strategy General information

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

Results

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

Search strategy

Database	Search terms		
Embase	No.	Query	Results
	#1	'contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage OR induced OR enhanced OR exposure OR administration OR iodinated OR iodine*)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti OR 'gadolinium-based':ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadavist:ti,ab OR gadodiamide:ti,ab OR gadopentetate:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR sonovue:ti,ab OR optison:ti,ab OR lumason:ti,ab OR definity:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR micropaque:ti,ab OR 'e-z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab OR visipaque:ti,ab OR hexabrix:ti,ab OR iomeron:ti,ab OR iopamiro:ti,ab OR omnipaque:ti,ab OR optiray:ti,ab OR ultravist:ti,ab OR xenetix:ti,ab OR iodixanol:ti,ab OR ioxaglate:ti,ab OR iomeprol:ti,ab OR iopamidol:ti,ab OR iosimenol:ti,ab OR iohexol:ti,ab OR ioversol:ti,ab OR iopromide:ti,ab OR iobitridol:ti,ab	28727
	#2	'myasthenia gravis'/exp OR ((myasthenia NEAR/2 gravis):ti,ab,kw)	27023
	#3	#1 AND #2 AND ([english]/lim OR [dutch]/lim) AND [2000-2021]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	73
	#4	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	699308
	#5	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3202960
	#6	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR	5842012

	'prospective study'/de OR 'cohort analysis'/de OR cohort*:ab,ti OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) #7 #3 AND #4 - SRs 1 #8 #3 AND #5 NOT #7 - RCTs 4 #9 #3 AND #6 NOT (#7 OR #8) – observational studies 14 #10 #7 OR #8 OR #9 19
Medline (OVID)	1 exp *Contrast Media/ or Barium/ or exp Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium-based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol).ti,ab,kf. (188788) 2 exp Myasthenia Gravis/ or (myasthenia adj2 gravis).ti,ab,kf. (19009) 3 1 and 2 (64) 4 limit 3 to ((english or dutch) and yr="2000 -Current") (37) 5 4 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (30) 6 (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (505387) 7 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2089139) 8 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (3654959) 9 5 and 6 (0) – SRs 10 (5 and 7) not 9 (2) - RCTs

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

6.4 Safe use of contrast media in patients with Mastocytosis

Validity and maintenance

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

Knowledge gaps

Ideally, the question whether systemic mastocytosis patients require anti-allergic premedication should be answered by means of a double blinded RCT with and without premedication. It is unlikely that such a trial will be funded.
Alternatively, mastocytosis drug allergy specialists could perform drug provocation tests in a safe setting in their entire cohort of mastocytosis patients to assess the risk of anaphylaxis/allergic reactions; after a negative provocation test, use of premedication should be discouraged.

Quality assurance indicators

Not applicable.

Implementation of recommendations

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

Evidence tables

Not applicable

Table of excluded studies

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

Literature search strategy

Search strategy

General information

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

Results

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

Search strategy

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

	OR hexabrix:ti,ab OR iomeron:ti,ab OR iopamiro:ti,ab OR omnipaque:ti,ab OR optiray:ti,ab OR ultravist:ti,ab OR xenetix:ti,ab OR iodixanol:ti,ab OR ioxaglate:ti,ab OR iomeprol:ti,ab OR iopamidol:ti,ab OR iosimenol:ti,ab OR iohexol:ti,ab OR ioversol:ti,ab OR iopromide:ti,ab OR iobitridol:ti,ab #2 'systemic mastocytosis'/exp OR 'mastocytosis'/exp OR mastocytos*:ti,ab,kw OR 57918 'mast cell*':ti,ab,kw #3 #1 AND #2 AND ([english]/lim OR [dutch]/lim) AND [2000-2021]/py NOT 103 (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) #4 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta 699308 analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab #5 'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 3202960 '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 #6 'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 5842012 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR cohort*:ab,ti OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) #7 #3 AND #4 - SRs 4 #8 #3 AND #5 NOT #7 - RCTs 9 #9 #3 AND #6 NOT (#7 OR #8) – observational studies 6 #10 #7 OR #8 OR #9 19
Medline (OVID)	1 exp *Contrast Media/ or Barium/ or exp Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium- based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or

	meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol).ti,ab,kf. (189146) exp Mastocytosis, Systemic/ or exp Mastocytosis/ or mastocytos*.ti,ab,kf. or 'mast cell*'.ti,ab,kf. (46193) 1 and 2 (248) limit 3 to ((english or dutch) and yr="2000 -Current") (141) 4 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (30) (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (505387) (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2089139) Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (3654959) 5 and 6 (2) – SRs (5 and 7) not 9 (4) - RCTs (5 and 8) not (9 or 10) (8) – observational studies 9 or 10 or 11 (14)

7. DM

7.1 Iodine-based CM and diabetes mellitus (DM)

Table of excluded studies

Table: Exclusion of article after examination of full text

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

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/not applicable	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

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Goergen, 2010 [individual study characteristics	SR and meta-analysis of [RCTs / cohort / case-control studies]	Inclusion criteria SR: 1) English language publication 2) administration of iodinated contrast medium in adult patients who were tacing metformin	Describe intervention: A: metformin and undergoing angiography	Describe control: A: not applicable B: not applicable	<u>End-point of follow-up</u>: A: not reported B: not reported C: not reported D: not reported	<u>Outcome measure-1</u> Defined as presence of metformin associated lactic acidosis (MALA), or relation between MALA and iodinated contrast medium administration	<u>Facultative</u>: Brief description of author’s conclusion: It is not clear whether cessation of metformin in patient undergoing

deduced from [1st author, year of publication] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	*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 outpatients <u>Source of funding:</u> Not reported	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 Impaired renal function: A; 4/33 (12%)	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,	C: not applicable D: not applicable	<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	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	intravascular contrast administration for radiological examination is effective for decreasing the risk of lactic acidosis and hyperglycaemia. 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.

		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	

8. CIE

8.1 Prevention of contrast-induced encephalopathy (CIE)

Validity and maintenance

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

Knowledge gaps

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

Quality assurance indicators

Not applicable.

Implementation of recommendations

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

Evidence tables

Not applicable

Table of excluded studies

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

Literature search strategy

Search strategy General information

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

Results

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

Search strategy

Database	Search terms		
Embase	No.	Query	Results
	#1	'contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage OR induced OR enhanced OR exposure OR administration OR iodinated OR iodine*)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti OR 'gadolinium-based':ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadavist:ti,ab OR gadodiamide:ti,ab OR gadopentetate:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR sonovue:ti,ab OR optison:ti,ab OR lumason:ti,ab OR definity:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR micropaque:ti,ab OR 'e-z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab OR visipaque:ti,ab OR hexabrix:ti,ab OR iomeron:ti,ab OR iopamiro:ti,ab OR omnipaque:ti,ab OR optiray:ti,ab OR ultravist:ti,ab OR xenetix:ti,ab OR iodixanol:ti,ab OR ioxaglate:ti,ab OR iomeprol:ti,ab OR iopamidol:ti,ab OR iosimenol:ti,ab OR iohexol:ti,ab OR ioversol:ti,ab OR iopromide:ti,ab OR iobitridol:ti,ab OR 'angiography'/exp OR angiogra*:ti,ab,kw OR 'angiogram'/exp	791221
	#2	'neurotoxicity'/exp/mj OR neurotoxi*:ti,ab,kw OR encephalopath*:ti,ab,kw	195191
	#3	#1 AND #2 AND ([english]/lim OR [dutch]/lim) AND [2001-2021]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	1534
	#4	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid)	714686

	NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab #5 'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 3323143 '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 #6 'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 6109921 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR cohort*:ab,ti OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) #7 #3 AND #4 - SRs 41 #8 #3 AND #5 NOT #7 - RCTs 91 #9 #3 AND #6 NOT (#7 OR #8) – observational studies 173 #10 #7 OR #8 OR #9 305
Medline (OVID)	exp Contrast Media/ or Barium/ or exp Microbubbles/ or exp Angiography/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium-based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol or angiogra*).ti,ab,kf. (553434) exp Neurotoxicity Syndromes/ or (neurotoxi* or encephalopath*).ti,ab,kf. (148307) 1 and 2 (2042) limit 3 to ((english or dutch) and yr="2001 -Current") (1214) 4 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (961) (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (480877) (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled

	clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2087471) Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (3656858) 5 and 6 (21) – SRs (5 and 7) not 9 (45) - RCTs (5 and 8) not (9 or 10) (182) – observational studies 9 or 10 or 11 (248)

9. IIHT

9.1 Prevention of Iodine-Induced Hyperthyroidism (IIHT) after use of iodine-based CM

Validity and maintenance

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

Knowledge gaps

- What are prevention strategies for Iodine-Induced Hyperthyroidism (IIHT) in previously specified risk groups:
- Patients with a history of cardiovascular disease and/or more than 65 years old
- Patients with a history of thyroid problems (goitre, hyperthyroidism, hypothyroidism)
- Patients who receive radioactive iodine treatment of the thyroid

Quality assurance indicators

Not applicable.

Implementation of recommendations

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

Evidence tables

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Fricke, 2004	Type of study: prospective comparative study Setting and country: Heart and Diabetes Center North Rhine-Westphalia, Bad Oeynhausen, Germany Funding and conflicts of interest: not reported.	Inclusion criteria: Patients admitted to the hospital for coronary angiography with a basal TSH level of less than 0.3 mU/l and normal levels of T3 and free T4 (fT4). Exclusion criteria: *Patients with immunogenic thyroid diseases, verified by the investigation of thyroid autoantibodies, as well as patients with thyroid-specific medication*. N total at baseline: Intervention (prophylactic medication based on results scintigraphy): 19 Control (no prophylactic medication): 56 Important prognostic factors[2]:	Describe intervention (treatment/procedure/test): *Coronary angiography was carried out with different amounts of iopromid (157±85 ml), containing 370 mg iodine per millilitre.* Previously described patients were treated 2 weeks with 900 mg perchlorate per day, divided into three doses, starting at least 3 hours before coronary angiography. *Depending on the autonomous volume, thiamazole was administered additionally. Twenty milligrams were given for 7 d if the autonomous volume was more than 5 ml and less than 10 ml. If the autonomous volume was greater than 10 ml, CA was performed only in patients with an urgent clinical indication. In those patients, 60 mg thiamazole was given for the first and 20 mg thiamazole for the second week.* *PDs were given according to the autonomous volume, in six patients perchlorate only, and in 13 patients a combined*	Describe control (treatment/procedure/test): *Coronary angiography was carried out with different amounts of iopromid (157±85 ml), containing 370 mg iodine per millilitre.* Previously described patients with normal thyroid function did not receive prophylactic medication.	Length of follow-up: 14 and 28 days after coronary angiography Loss-to-follow-up: Loss-to-follow-up: Intervention, N (%): 2 Reasons (describe): In one case, coronary angiography was not performed because of high autonomous volume. In another case, contrast agent was given a second time for angioplasty. Control, N (%): 14 Reasons (describe): because of the lack of feedback from the general practitioner. Incomplete outcome data: Intervention: not reported Control: not reported	Outcome measures and effect size (include 95%CI and p-value if available): 1.1 Iodine-induced hyperthyroidism *Definition IIHT not reported* I: 2/19 (10.5%) C: 0/56 (0%) 2. Iodine induced hypothyroidism Not reported	Authors conclusion: *Scintigraphy of the thyroid gland is suitable for risk stratification of iodine- induced hyperthyroidism in patients with low TSH undergoing CA. Up to a thyroid uptake (TCTU) of 1%, the risk of iodine-induced hyperthyroidism is negligible, and CA can be performed without administration of PDs. The kind, dosage, and duration of prophylactic therapy in case of the TCTU being higher is still a matter calling for further investigation.*

		No prophylactic medication was given based on scintigraphy under the following circumstances: *1) homogenous tracer distribution in the thyroid, TCTU less than 1.5%, and basal TSH ranging from 0.05 to less than 0.3; 2) homogenous tracer distribution in the thyroid,* *TCTU less* *than 1.0%, and basal TSH less than 0.05; and* *3) focal uptake indicating focal autonomy and TCTU less than 1.0%.* Group characteristics not described (age, gender) at baseline. *Thyroid volume at baseline* *I: 35.1 ± 16.2 ml* *C: 27.6 ± 15.6 ml* *There was no major difference in the frequency of thyroid* *nodules or changes of echogenicity of the thyroid gland*	*therapy with thiamazole.*				

		within the two groups.					
Nolte, 1996	Type of study: prospective randomized study Setting and country: Georg-August-Universität, Göttingen, Germany Funding and conflicts of interest: *Partially supported by the Forum Schilddrüse e.V., Hamburg, Germany.* No conflicts of interest reported.	Inclusion criteria: patients from a iodine deficient area in Germany who were admitted to the hospital for coronary angiography and had euthyroid autonomy defined as: *normal FT3 index and normal FT4 index, delta-TSH < 3.5 //U/ml and a 99mTc uptake (TcU) of more than 1.1% (in order to exclude patients with concurrent iodine contamination for other reasons).* Exclusion criteria: *manifest hyperthyroidism, large autonomous adenoma, immunogenic thyroid disease, urine iodine excretion of more than 200iimol/mol creatinine, instable angina pectoris, second disease with a Karnofsky index of less than*	Describe intervention (treatment/procedure/test): *The mean volume of contrast medium was 149ml and ranged from 50 to 410ml.* *Treatment was begun 1 day before angiography and lasted for 14 days* *Group 1 received 20 mg of thiamazole once a day* *Group 2 was treated with 900 mg of sodium perchlorate (300 mg three times a day)*	Describe control (treatment/procedure/test): *The mean volume of contrast medium was 149ml and ranged from 50 to 410ml.* *Group 3 represented the control group and received no special therapy*	Length of follow-up: 30 days Loss-to-follow-up: Intervention: not reported Control: not reported Incomplete outcome data: Intervention: not reported Control: not reported	Outcome measures and effect size (include 95%CI and p-value if available): Iodine-induced hyperthyroidism *Defined as suppressed TSH and increased FT41 and/or FT3I* Group 1: 1/17 Group 2: 1/17 Group 3: 2/17 2. Iodine induced hypothyroidism *Defined as increased TSH and reduced FT4f 30 days after coronary angiography* Group 1: 0 Group 2: 0 Group 3: 0	Authors conclusion: *The present study shows that in patients with euthyroid functional autonomy and increased risk for the development of iodine-induced hyperthyroidism, thiamazole and sodium perchlorate have some protective effect during iodine contamination when given prophylactically. Thirty days after CA the following effects of prophylactic short- term treatment were seen.* *Despite these significant effects, one patient with a small and short-term elevation of thyroid hormones was observed in each of the treated groups. This implies that both drugs at the applied doses were not able to totally prevent thyrotoxicosis.* *As hyperthyroidism could not be prevented totally by monotherapy with either thionamide or perchlorate, a combination therapy with thionamide and sodium perchlorate in risk patients could be more effective and should be*

		50%, patients older than 75 years or younger than 40 years, application of contrast media in the last 6 months and the concomitant use of thyroid hormones, thyrostatic drugs or amiodarone. <u>N total at baseline</u>: Intervention group 1 (Thiamazole): 17 Intervention group 2 (Perchlorate): 17 Control group 3: 17 <u>Important prognostic factors</u>: *There was no significant difference between groups 1, 2 and 3 with regard to age, sex, mean volume of contrast media and goitre size. Side effects of thyrostatic drugs were not observed. N.B. Thyroid volume was increased on average (mean 54.4ml, range 16.3-180ml):*					*tested in further trials.*

		25% of patients showed nodulous goitres, 67% had diffuse goitres and 8% showed a normal thyroid gland.					

Risk of bias table

Study reference	Bias due to a non-representative or ill-defined sample of patients?	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?	Bias due to ill-defined or inadequately measured outcome?	Bias due to inadequate adjustment for all important prognostic factors?
Fricke, 2004	Unlikely, patients were well described	Unclear, no differences in follow up between groups, however missing values were not reported	Unclear, the main outcome IIHT was not defined in the article. The exact numbers were not reported for the outcomes free T3 and T4.	Likely, patients were not comparable due to the selection with scintigraphy. The authors did not adjust for prognostic factors.
Nolte, 1996	Unlikely, patients were well described	Unclear, no differences in follow up between groups, however missing values were not reported	Unlikely, the outcome measures were clearly defined.	Unclear, prognostic factors were not described.

Table of excluded studies

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

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

Literature search strategy

Search strategy General information

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

Results

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

Search strategy

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

		gadopentetate:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR sonovue:ti,ab OR optison:ti,ab OR lumason:ti,ab OR definity:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR micropaque:ti,ab OR 'e-z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab OR visipaque:ti,ab OR hexabrix:ti,ab OR iomeron:ti,ab OR iopamiro:ti,ab OR omnipaque:ti,ab OR optiray:ti,ab OR ultravist:ti,ab OR xenetix:ti,ab OR iodixanol:ti,ab OR ioxaglate:ti,ab OR iomeprol:ti,ab OR iopamidol:ti,ab OR iosimenol:ti,ab OR iohexol:ti,ab OR ioversol:ti,ab OR iopromide:ti,ab OR iobitridol:ti,ab	
	#2	'hyperthyroidism'/exp OR hyperthyroid*:ti,ab,kw OR hyperthyreoid*:ti,ab,kw OR hyperthyreosis:ti,ab,kw OR 'thyroid gland hyperfunction':ti,ab,kw OR 'thyroid hyperfunction':ti,ab,kw OR 'thyroideal hyperfunction':ti,ab,kw OR thyreotoxicosis:ti,ab,kw OR 'thiamazole'/exp OR 'perchlorate'/exp OR thiamazole:ti,ab,kw OR methimazole:ti,ab,kw OR perchlorate:ti,ab,kw	89224
	#3	#1 AND #2 AND ([english]/lim OR [dutch]/lim) AND [1990-2021]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	655
	#4	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	714686
	#5	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3323143
	#6	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR cohort*:ab,ti OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6109921
	#7	#3 AND #4 - SRs	13
	#8	#3 AND #5 NOT #7 - RCTs	83

	#9 #3 AND #6 NOT (#7 OR #8) – observational studies 64 #10 #7 OR #8 OR #9 160
Medline (OVID)	exp Contrast Media/ or Barium/ or exp Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or 'radiopaque medi*' or barium or gadolinium or microbubble* or 'gadolinium- based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or meglumine or dimeglumine or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol).ti,ab,kf. (232746) exp Hyperthyroidism/ or exp Methimazole/ or exp Perchlorates/ or (hyperthyroid* or hyperthyreoid* or hyperthyreosis or 'thyroid gland hyperfunction' or 'thyroid hyperfunction' or 'thyroideal hyperfunction' or thyreotoxicosis or thiamazole or methimazole or perchlorate*).ti,ab,kf. (61397) 1 and 2 (555) limit 3 to ((english or dutch) and yr="1990 -Current") (323) 4 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (256) (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (480877) (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2087471) Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (3656858) 5 and 6 (2) – SRs (5 and 7) not 9 (22) - RCTs (5 and 8) not (9 or 10) (44) – observational studies 9 or 10 or 11 (68)

10. Safe time intervals and analytical interference

10.1 Multiple investigations with contrast media in patients with normal or reduced kidney function

Validity and maintenance

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

Knowledge gaps

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

Quality assurance indicators

Not applicable.

Implementation of recommendations

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

Evidence tables

Not applicable

Table of excluded studies

Not applicable

Literature search strategy

General information

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

Results

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

Search strategy

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

		hexafluoride:ti OR micropaque:ti OR 'e-z cat':ti OR polibar:ti OR barite:ti OR baritop:ti OR visipaque:ti OR hexabrix:ti OR iomeron:ti OR iopamiro:ti OR omnipaque:ti OR optiray:ti OR ultravist:ti OR xenetix:ti OR iodixanol:ti OR ioxaglate:ti OR iomeprol:ti OR iopamidol:ti OR iosimenol:ti OR iohexol:ti OR ioversol:ti OR iopromide:ti OR iobitridol:ti OR iopentol:ti OR ioxithalamate:ti	
	#2	'pharmacokinetics'/exp/mj OR pharmacokinetic*:ti OR 'biodistribution'/exp/mj OR biodistribution:ti OR washin:ti OR 'wash in':ti OR washout:ti OR 'wash out':ti OR 'urinary excretion'/exp/mj OR (((kidney OR renal) NEAR/3 (excretion OR elimination)):ti) OR 'half life':ti	323271
	#3	'plasma concentration-time curve'/exp OR ((time NEAR/3 (interval OR point* OR curve)):ti,ab,kw) OR hour*:ti,ab,kw OR day*:ti,ab,kw	3858138
	#4	iopanoate:ti OR iodoxamate:ti OR ioglycamate:ti OR ioglycamide:ti OR iodipamide:ti OR iotroxamide:ti OR cholecystography:ti OR cholecystographic:ti OR cholecystopaques:ti OR fluorescein:ti OR fluoresceinated:ti OR sisomicin:ti OR penicillin:ti OR azlocillin:ti OR gentamycin:ti OR tobramycin:ti OR ciprofloxacin:ti OR cefotaxime:ti	46950
	#5	#1 AND #2 AND #3 AND ([english]/lim OR [dutch]/lim) AND [1975-2021]/py NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT #4	388
	#6	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	699308
	#7	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3202960
	#8	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR cohort*:ab,ti OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	5842012
	#9	#5 AND #6 - SRs	3
	#10	#5 AND #7 NOT #6 - RCTs	64
	#11	#5 AND #8 NOT (#9 OR #10) – observational studies	22
	#12	#9 OR #10 OR #11	89

	#13 #5 NOT #12 – other study designs 299
Medline (OVID)	exp *Contrast Media/ or *Barium/ or exp *Microbubbles/ or (((contrast or radiocontrast) adj2 (medi* or agent* or material* or dose or doses or dosage or induced or enhanced or exposure or administration or iodinated or iodine*)) or barium or gadolinium or microbubble* or 'gadolinium-based' or gbca* or primovist or eovist or omniscan or magnevist or optimark or prohance or multihance or dotarem or gadovist or gadavist or clariscan or gadodiamide or gadopentetate or gadoversetamide or gadoteridol or gadobenate or gadoterate or gadobutrol or 'gadoxetic acid' or 'gadoxetate disodium' or gadopiclenol or 'gd dtpa' or 'gd hp do3a' or 'gd dtpa bma' or 'gd dota' or 'gd dtpa bmea' or 'gd bopta' or 'gd bt do3a' or 'gd eob dtpa' or sonovue or optison or lumason or definity or perflutren or hexafluoride or micropaque or 'e-z cat' or polibar or barite or baritop or visipaque or hexabrix or iomeron or iopamiro or omnipaque or optiray or ultravist or xenetix or iodixanol or ioxaglate or iomeprol or iopamidol or iosimenol or iohexol or ioversol or iopromide or iobitridol or iopentol or ioxithalamte).ti. (81162) exp *Pharmacokinetics/ or (pharmacokinetic* or biodistribution or washin or 'wash in' or washout or 'wash out' or ((kidney or renal) adj3 (excretion or elimination)) or 'half life').ti. (120566) ((time adj3 (interval or point* or curve)) or (hour* or day*)).ti,ab,kf. (2621752) (iopanoate or iodoxamate or ioglycamate or ioglycamide or iodipamide or iotroxamide or cholecystography or cholecystographic or cholecystopaque* or fluorescein or fluoresceinated or sisomicin or penicillin or azlocillin or gentamycin or tobramycin or ciprofloxacin or cefotaxime).ti. (42942) (1 and 2 and 3) not 4 (201) limit 5 to ((english or dutch) and yr="1975 -Current") (192) 6 not (comment/ or editorial/ or letter/) (192) meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf. (509388) (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2097343) Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (3672356) 7 and 8 (2) – SRs (7 and 9) not 11 (35) - RCTs (7 and 10) not (11 or 12) (23) – observational studies 11 or 12 or 13 (60)

	15 7 not 14 (132) – other study designs

10.2 Analytical interference of contrast media with clinical laboratory tests

Validity and maintenance

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

Knowledge gaps

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

Quality assurance indicators

Not applicable

Implementation of recommendations

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

Evidence tables

Not applicable

Table of excluded studies

Not applicable

Literature search strategy

Not applicable

11. Other safety measures

11.1 CM administration using power injectors

Knowledge Gaps
It is not clear what the safety and efficacy is of contrast administration with haemodialysis catheters versus peripheral intravenous access sites.

It is not clear what the effect is on image quality when contrast power injection is performed using CVCs, HD catheters, PICCs and TIVAPs versus peripheral catheters.

Quality Indicators
None.

Implementation

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
Use a peripheral venous access catheter for IV power injected contrast administration to obtain the best quality level of contrast images.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
Check the position of the CVC TIVAD or PICC line and its patency before and after the power injected contrast administration, when a peripheral venous access catheter is unavailable.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
When optimal quality of contrast-	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

enhanced images in CT is needed, the use of a power injector and a peripheral venous access catheter for IV contrast administration is recommended.							
Power-injectable central venous catheters may be safely used for administration of CM using a power injector, when recommendations of the catheter manufacturer are followed.	1-3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
Power-injectable haemodialysis catheters may be safely used for administration of CM using a power injector, when recommendations of the catheter manufacturer are followed.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
There is a risk of catheter tip migration of PICCs and TIVADs when CM is injected via a power injector in patients with a catheter tip position above the tracheobronchial angle.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

When a power-injectable PICC or TIVAD is used for CM administration, check the position of the catheter tip with a CT scout radiograph before and after power-injection of CM.							
When a power-injectable CVC, HC, PICC or TIVAD is used for CM administration with a power injector, check the patency of the catheter after the procedure by manual flush of 20ml normal saline.	1-3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.
[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.
[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Evidence tables

Not applicable, none of the studies fulfilled the inclusion criteria of the PICO.

Exclusion Table

Table Exclusion after full text review

Author and Year	Reasons for exclusion
Uslusoy, 2008	Does not fulfil PICO-criteria.
Teichgräber, 2011	Does not fulfil PICO-criteria.
Klee, 2011	Does not fulfil PICO-criteria: Pediatric population
Coyle, 2004	Included in SR Buijs, 2017
Herts, 2001	Included in SR Buijs, 2017
Kaste, 1996	Does not fulfil PICO-criteria.
Verity, 2017	Small sample size
Morden, 2014	Included in Buijs, 2017
Hardie, 2014	Does not fulfil PICO-criteria
MAcHt, 2012	Included in Buijs, 2017
Goltz, 2012	Included in Buijs, 2017

Alexander, 2012	No full-tekst available
Goltz, 2011	Included in Buijs, 2017
Wienbeck, 210	Does not fulfil PICO-criteria

Search strategy

Database	Search terms	Total
PubMed 1996 – May 2018	((("Contrast Media"[Mesh] OR contrast [tiab] OR radiocontrast [tiab] OR radiopaque [tiab] OR "Barium"[Mesh] OR barium [tiab] OR gadolinium [tiab] OR microbubble* [tiab]) AND ("Central Venous Catheters"[Mesh] OR "Catheterization, Central Venous"[Mesh] OR "Catheterization, Peripheral"[Mesh] OR "Vascular Access Devices"[Mesh] OR venous catheter* [tiab] OR central catheter* [tiab] OR Central line* [tiab] OR PICC [tiab] OR PICCs [tiab] OR CVP [tiab] OR central venous line* [tiab] OR CVC [tiab] OR CVL [tiab] OR PAC [tiab] OR port [tiab] OR ports [tiab] OR port-a-cath [tiab] OR hickman* [tiab] OR vein catheter* [tiab] OR CVAD* [tiab] OR vascular access device* [tiab] OR broviac [tiab]) AND (pump*[tiab] OR power inject*[tiab])) AND ("1996/01/01"[PDat] : "3000/12/31"[PDat]) AND English[lang]) = 82	= 96
Embase (Elsevier)	('contrast medium'/exp OR contrast:ti,ab OR radiocontrast:ti,ab OR radiopaque*:ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti) AND ('central venous catheter'/exp OR 'vascular access device'/exp OR 'venous catheter*':ti,ab OR 'central catheter*':ti,ab OR 'central line*':ti,ab OR picc*:ti,ab OR cvp:ti,ab OR 'central venous line*':ti,ab OR cvc:ti,ab OR cvl:ti,ab OR pac:ti,ab OR port:ti,ab OR ports:ti,ab OR 'port-a-cath':ti,ab OR hickman*:ti,ab OR 'vein catheter':ti,ab OR cvad*:ti,ab OR 'vascular access device*':ti,ab OR broviac:ti,ab) AND (pump*:ti,ab OR 'power inject*':ti,ab) AND [english]/lim AND [1996-2018]/py NOT 'conference abstract':it = 80	

11.2 Optimal treatment of CM extravasation

Knowledge Gaps

It is not clear what the best treatment is for contrast extravasation, and if any treatment is effective at all.

Indicators

None.

Implementation

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks

Consider the following treatment options for contrast extravasation: Try to aspirate the extravasated contrast medium through an inserted needle Mark affected area Use compresses, for relieving pain at the injection site Use pain killers Elevate the affected extremity above the level of the heart.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
Record contrast extravasation and treatment in the patient record (volume, CM concentration, area, clinical findings).	1-3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
Give the patient clear instructions when to seek additional medical care: Any worsening of symptoms Skin ulceration Development of any neurologic or circulatory symptoms, including paraesthesia's Give the patient a patient	1-3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

information leaflet.							
For severe extravasation injury: Consult a plastic surgeon Notify the referring physician.	1-3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.
[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.
[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Table of excluded studies

Table Exclusion after reading the full text

Author and year	Reasons for exclusion
Bellin 2002	Does not fulfil selection criteria. No control group. Descriptive.
Botany 2010	Does not fulfil selection criteria. No control group. Descriptive.
Cochran 2002	Does not fulfil selection criteria. No control group. Descriptive.
Cohan 1997	Does not fulfil selection criteria. No control group. Descriptive.
Conner 2017	Does not fulfil selection criteria. No control group. Descriptive.
Conner 2017	Does not fulfil selection criteria. No control group. Descriptive.
Davenport 2012	Does not fulfil selection criteria. No control group. Descriptive.
Ding 2018	Does not discuss treatment of extravasation
Ding 2018	Does not fulfil selection criteria. No control group. Descriptive.
Earhart 2011	Does not fulfil selection criteria. No control group. Descriptive.
Fallscheer 2007	Does not fulfil selection criteria. No control group. Descriptive.
Kim 2017	Does not fulfil selection criteria. No control group. Descriptive.
Kim 2017	Does not fulfil selection criteria. No control group. Descriptive.
Nicola 2016	Does not fulfil selection criteria. No control group. Descriptive.
Rose 2015	Does not fulfil selection criteria. No control group. Descriptive.
Schaverien 2008	Does not fulfil selection criteria. No control group. Descriptive.
Schummer 2010	Does not fulfil selection criteria. No control group. Descriptive.
Sonis 2017	Does not fulfil selection criteria. No control group. Descriptive.
Sonis 2017	Does not fulfil selection criteria. No control group. Descriptive.
Sum 2006	Does not fulfil selection criteria. No control group. Descriptive.
Tonolini 2012	Does not fulfil selection criteria. No control group. Descriptive.
Tonolini 2016	No comparison therapies. Letter to the editor on the occasion of Nicola 2016
Tsai 2007	Does not fulfil selection criteria. No control group. Descriptive.
Vandeweyer 2000	Does not fulfil selection criteria. No control group. Descriptive.
Wang 2007	Does not fulfil selection criteria. No control group. Descriptive.
Wilson 2011	Does not fulfil selection criteria. No control group. Descriptive.

Literature search strategy

Database	Search strings	Total
PubMed 1996 – February 2018	(("Extravasation of Diagnostic and Therapeutic Materials"[Mesh] OR extravasation*[tiab] OR compartment syndrome*[tiab]) AND ("Contrast Media"[Majr] OR contrast medi*[ti])) AND (("1996/01/01"[PDat] : "3000/12/31"[PDat]) AND (English[lang] OR Dutch[lang])) *Systematic Review filter:* (systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR "cochrane database syst rev"[Journal] OR "Evidence	480

	report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt]) *RCT filter:* ((random*[tiab] AND (controlled[tiab] OR control[tiab] OR placebo[tiab] OR versus[tiab] OR versus[tiab] OR group[tiab] OR groups[tiab] OR comparison[tiab] OR compared[tiab] OR arm[tiab] OR arms[tiab] OR crossover[tiab] OR cross-over[tiab]) AND (trial[tiab] OR study[tiab])) OR ((single[tiab] OR double[tiab] OR triple[tiab]) AND (masked[tiab] OR blind*[tiab]))) OR ((random*[ot] AND (controlled[ot] OR control[ot] OR placebo[ot] OR versus[ot] OR versus[ot] OR group[ot] OR groups[ot] OR comparison[ot] OR compared[ot] OR arm[ot] OR arms[ot] OR crossover[ot] OR cross-over[ot]) AND (trial[ot] OR study[ot])) OR ((single[ot] OR double[ot] OR triple[ot]) AND (masked[ot] OR blind*[ot]))) = 319	
Embase (Elsevier)	(('extravasation'/exp OR extravasation*:ab,ti OR 'compartment syndrom*':ab,ti) AND ('contrast medium'/exp/mj OR 'contrast medi*':ti) AND ([dutch]/lim OR [english]/lim) AND [1996-2018]/py) NOT 'conference abstract':it)) *Systematic Review filter*: (('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo: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))) *RCT filter*: (('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)) = 319	

Evidence tables

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