

Guideline Safe Use of Contrast Media Part 1

This part 1 comprises:

- 1. Prevention of post-contrast acute kidney injury**
- 2. Use of iodine-containing contrast media in patients with diabetes type 2 who use metformin**
- 3. Use of iodine-containing contrast media in patients undergoing dialysis**

INITIATED BY

Radiological Society of the Netherlands

IN ASSOCIATION WITH

Netherlands Association of Internal Medicine
Dutch Federation for Nephrology
Dutch Society of Intensive Care
Association of Surgeons of the Netherlands
The Netherlands Society of Cardiology
Dutch Society for Clinical Chemistry and Laboratory Medicine
Netherlands Society of Emergency Physicians
Dutch Association of Urology
Dutch Society Medical Imaging and Radiotherapy

WITH THE ASSISTANCE OF

Knowledge Institute of Medical Specialists

FINANCED BY

Quality Funds of Medical Specialists

Colophon

GUIDELINE SAFE USE OF CONTRAST MEDIA – PART 1

©2017

Radiological Society of the Netherlands

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Chapter 1 General Introductions

General Introduction New Guideline Set on Safe Use of Contrast Media

The Radiological Society of The Netherlands (RSTN - NVvR) deemed a set of new guidelines on the Safe Use of Contrast Media (CM) highly necessary and relevant, due to recent publications on many topics concerning contrast safety. Because of recent scientific developments, the recommendations of the most recent CM guideline (CBO, 2007) were in conflict with what should be considered best clinical practice. In order to update this 2007 CBO Guideline, which only covered selected topics on the use of iodine-containing CM, a plan has been developed to make a set of 3 new guidelines covering the safe use of all types of CM in adults.

The patient population for which these guidelines are meant consists of adult patients (>18 years) who receive intravascular, oral or intracavitary (intra-articular, intra-vesical, intra-cholangiographic) iodine-containing contrast media both in the clinical setting, as well as for outpatients. The guidelines do not cover radioactive contrast media use in nuclear medicine.

The three parts of the Safe Use of Contrast Media guidelines will be produced in three consecutive 2-year projects and will cover the following topics regarding CM safety (part 3 is still in the planning phase, topics to be finalized):

Safe Use of Contrast Media - Part 1 (2014-2017):

- prevention of post-contrast acute kidney injury (PC-AKI) from iodine-containing contrast media;
- iodine-containing contrast media use in patients with type-2 diabetes taking metformin;
- iodine-containing contrast media use in patients on chronic dialysis.

Safe Use of Contrast Media - Part 2 (2016-2019):

- management of hypersensitivity reactions to contrast media;
- prophylaxis of hypersensitivity reactions to contrast media & the role of skin testing in patients with hypersensitivity reactions;
- contrast media injections with power injectors through (peripherally inserted) central venous lines and implantable ports;
- contrast media extravasation;
- nephrotoxicity of gadolinium-based contrast agents;
- prevention of nephrogenic systemic fibrosis (NSF);
- retention of gadolinium in the body after use of gadolinium-based contrast agents.

Safe Use of Contrast Media - Part 3 (2018-2020; still in planning):

- prevention of iodine-induced hyperthyroidism;
- safety of organ-specific gadolinium-based contrast agents;
- contrast media use in pregnancy and during lactation;
- contrast media use in patients with pheochromocytoma;
- contrast media use in patients with myasthenia gravis;
- contrast media use in patients with mastocytosis;
- the Weber and Lalli effects in using contrast media.

General Introduction Part 1

This first part will deal with one of the main challenges in the intravenous and intra-arterial use of CM, the prevention of contrast-induced nephropathy (CIN), also called contrast-induced acute kidney injury (CI-AKI). This issue has received large interest in recent years, resulting in strict prevention guidelines for all physicians requesting radiologic or cardiologic diagnostic or interventional studies with iodine-containing CM. The nephrotoxicity of gadolinium-based contrast media and/or microbubble contrast media and the recommendations for measurement of eGFR will be integrated with the guidelines for prevention of Nephrogenic Systemic Fibrosis. These recommendations will be published in the guideline Safe Use of Contrast Media, part 2 (due begin 2019).

The mainstay of the current prevention protocols consists of intravenous volume expansion with either normal saline (NaCl 0.9%), lactated Ringer's solution, or sodium bicarbonate (NaHCO₃ 1.4%), starting multiple hours before the administration of iodine-containing CM and continuing for multiple hours after iodine-containing CM administration. The time intervals for this preventive hydration normally range from 4-12 hours before and 4-12 hours after iodine-containing contrast administration, but these may have to be individualized and prolonged in patients with severe congestive heart failure or in patients with severe renal failure.

Obviously, such protocols present a logistic and financial burden to the hospital system (Kooiman, 2013). To admit all patients at increased risk for AKI in day-hospital wards for intravenous volume expansion is expensive, and the volume expansion itself may lead to complications as well.

Despite the large amount of medical literature produced, researchers in the USA in 2006 began to question the causative role of iodine-containing CM in post-contrast acute kidney injury (PC-AKI). They noted that when studies with proper control populations were analysed, the role of intravenously-injected CM as a cause for AKI was largely overestimated, since changes in serum creatinine that fulfilled the definition of contrast-induced nephropathy (CIN) were found at the same frequency in patients who did not receive CM (Bruce, 2009; Katzberg, 2007; Newhouse, 2008; Rao, 2006).

Researchers from the Mayo Clinic and the University of Michigan, centers with an extensive focus on CM research by tradition, subsequently performed a number of large retrospective, observational studies with control populations selected by the strict process of propensity-score matching (Austin, 2011; McDonald, 2013), in order to solve this problem. These studies focused on intravenous injection of CM in patients undergoing computed tomography (CT) and showed a much lower risk of PC-AKI than previously expected (Davenport, 2013; McDonald, 2014; McDonald, 2015).

Goal of the current guideline

The aim of the Part 1 of Safe Use of Iodine-containing Contrast Media guidelines is to critically review the present recent evidence with the above trend in mind, and try to formulate new practical guidelines for all hospital physicians to provide the safe use of contrast media in diagnostic and interventional studies. The ultimate goal of this

guideline is to increase the quality of care, by providing efficient and expedient healthcare to the specific patient populations that may benefit from this healthcare and simultaneously guard patients from ineffective care. Furthermore, such a guideline should ideally be able to save money and reduce day-hospital waiting lists.

Focus of the guideline

This part 1 of the Safe Use of Contrast Media guideline focuses on all adult (18 years and older) patients that receive iodine-containing CM during radiologic or cardiologic studies or interventions.

Post-contrast AKI is predominantly an issue of iodine-containing CM and to a lesser degree related to the use of gadolinium-based contrast media for MRI and is no issue for microbubble contrast media for ultrasound.

The techniques involved include contrast-enhanced studies in computed tomography, and (cardio) angiography. Magnetic resonance imaging and ultrasound will be discussed in Part 2 of the Safe Use of Contrast Media Guideline.

The primary outcome measures in PC-AKI are a decrease in estimated glomerular filtration rate (eGFR) or an increase in serum creatinine (sCr).

Secondary measures are the incidence of renal replacement therapy, days of admittance in hospital, associated patient morbidity and mortality and costs.

Users of this guideline

This guideline is intended for all hospital physicians that request or perform diagnostic or interventional radiologic or cardiologic studies for their patients in which CM are involved.

Terminology and definitions

Because of the recent developments there is confusion about terminology. Terms as post-contrast acute kidney injury, contrast-associated acute kidney injury, and contrast-induced acute kidney injury or contrast-induced nephropathy are incorrectly used interchangeably.

Therefore, this guideline will follow the American College of Radiology (ACR) Committee on Drugs and Contrast Media that has published the following suggestion for more uniformity (ACR Manual, 2017):

Post-contrast acute kidney injury (PC-AKI) is a general term used to describe a sudden deterioration in renal function that occurs within 48 hours following the intravascular administration of iodine-containing CM. PC-AKI may occur regardless of whether the CM was the cause of the deterioration. PC-AKI is a correlative diagnosis.

Contrast-induced acute kidney injury (CI-AKI) or contrast-induced nephropathy (CIN) is a specific term used to describe a sudden deterioration in kidney function that is caused

by the intravascular administration of iodine-containing CM; therefore, CI-AKI/CIN is a subgroup of PC-AKI. CI-AKI/CIN is a causative diagnosis.

The ACR acknowledges that very few published studies have a suitable control group to permit the separation of CI-AKI/CIN from PC-AKI. Therefore, the incidence of PC-AKI reported in clinical studies and the incidence of PC-AKI observed in clinical practice likely includes a combination of CI-AKI (i.e., AKI caused by CM administration) and AKI unrelated to CM administration (i.e., AKI coincident to but not caused by CM administration).

Therefore, PC-AKI and CI-AKI are not interchangeable (ACR Manual, 2017).

Clinical Course and Incidence

Post-contrast acute kidney injury (PC-AKI) is an iatrogenic renal injury that follows intravascular administration of contrast media (CM) in susceptible individuals (Rear, 2016).

It is difficult to distinguish between different aetiologies of acute kidney injury. In most of cases PC-AKI is mild and reversible with returning of renal function to baseline or near baseline values within 1 to 3 weeks. (Gutterez, 2002; Mehran, 2006) As common for all forms of AKI, the occurrence of PC-AKI has shown to be a marker for increased short- and long-term morbidity and mortality and longer duration of hospital stay (Gruberg, 2000; Gupta, 2005; Kooiman, 2015; Mitchell, 2015).

Various studies suggest that the route of administration of CM (intra-arterial versus intravenous) and type of procedure (i.e. catheter-based angiography versus CT imaging) can have a substantial impact on the incidence of PC-AKI (Dong, 2012; Solomon, 2008).

Guideline Disclaimers

General

The aim of clinical guidelines is to help clinicians to make informed decisions for their patients. However, adherence to a guideline does not guarantee a successful outcome. Ultimately, healthcare professionals must make their own treatment decisions about care on a case-by-case basis, after consultation with their patients, using their clinical judgement, knowledge and expertise. A guideline cannot replace a physician's judgment in diagnosing and treatment of particular patients.

Guidelines may not be complete or accurate. The Working Group of this guideline and members of their boards, officers and employees disclaim all liability for the accuracy or completeness of a guideline, and disclaim all warranties, express or implied to their incorrect use.

Guidelines users always are urged to seek out newer information that might impact the diagnostic and treatment recommendations contained within a guideline.

Individualisation

In specific high-risk patient groups (e.g. in patients with high-grade congestive heart failure or end-stage chronic kidney disease) clinicians may have to regress from these

general guidelines and decide on individualisation of preventive measures to best fit the needs of their patients.

Life-threatening situations or conditions

In acute life-threatening situations or conditions clinicians may have to regress from these general guidelines and decide on individualisation of renal function estimation or preventive measures to best fit the needs of their patients in these situations or conditions.

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Chapter 2 Justification of this Guideline

Validity

The board of the Radiological Society of the Netherlands will determine at the latest in 2023 if this guideline (per module) is still valid and applicable. If necessary, a new working group will be formed to revise the guideline. The validity of a guideline can be shorter than 5 years, if new scientific or healthcare structure developments arise, that could be seen as a reason to commence revisions. The Radiological Society of the Netherlands is considered the keeper of this guideline and thus primarily responsible for the actuality of the guideline. The other scientific societies that have participated in the guideline development share the responsibility to inform the primarily responsible scientific society about relevant developments in their field.

Initiative

Radiological Society of the Netherlands

Authorization

The guideline is submitted for authorization to:

- Radiological Society of the Netherlands
- Netherlands Association of Internal Medicine
- Dutch Federation of Nephrology
- Dutch Society of Intensive Care
- Association of Surgeons of the Netherlands
- Netherlands Society of Cardiology
- Netherlands Society for Clinical Chemistry and Laboratory Medicine
- Netherlands Society of Emergency Physicians
- Dutch Association of Urology
- Dutch Society Medical Imaging and Radiotherapy

General Information

The guideline development was assisted by the Knowledge Institute of Medical Specialists (www.kims.orde.nl) and was financed by the Quality Funds for Medical Specialists (Kwaliteitsgelden Medisch Specialisten: SKMS).

Working group members

A multidisciplinary working group was formed for the development of the guideline in 2014. The working group consisted of representatives from all relevant medical specialization fields that are involved with intravascular contrast administration.

All working group members have been officially delegated for participation in the working group by their scientific societies. The working group has developed a guideline in the period from October 2014 until July 2017.

The working group is responsible for the complete text of this guideline.

Conflicts of interest

The working group members have provided written statements about (financially supported) relations with commercial companies, organisations or institutions that are related to the subject matter of the guideline. Furthermore, inquiries have been made regarding personal financial interests, interests due to personal relationships, interests related to reputation management, interest related to externally financed research and interests related to knowledge valorisation. The statements on conflict of interest can be requested at the administrative office of the Knowledge Institute of Medical Specialists and are summarised below.

Member	Function	Other offices	Personal financial interests	Personal relationships	Reputation management	Externally financed research	Knowledge-valorisation	Other potential conflicts of interest	Signed
Workgroup									
Van der Molen	Chairman, radiologist	Member Contrast Media Safety Committee of the European Society of Urogenital Radiology (unpaid, CMSC meetings are partially funded by CM industry))	None	None	Secretary section of Abdominal Radiology; Radiological Society of the Netherlands (until spring of 2015)	None	None	Receives Royalties for books: Contrast Media Safety, ESUR guidelines, 3 rd ed. Springer, 2015 Received speaker fees for lectures on CM safety by GE Healthcare, Guerbet, Bayer Healthcare and Bracco Imaging (2015-2016)	Yes
Geenen	Member, radiologist	Member Contrast Media Safety Committee of the European Society of Urogenital Radiology (unpaid, meetings are partially funded by CM industry)))	None	None	None	None	None	Has been a public speaker during symposia organised by GE Healthcare about contrast agents (most recently in June 2014)	Yes
Dekker	Member, radiologist	None	None	None	None	None	None	None	Yes
Pels Rijcken	Member, interventional radiologist	None	None	None	None	None	None	None	Yes
Danse	Member, cardiologist	Board member committee of Quality, Dutch society for Cardiology (unpaid) Board member Conference committee DRES (unpaid)	None	None	None	None	None	None	Yes
Oudemans	Member, intensive	none	None	None	None	None	None	None	Yes

– van Straaten	care medical specialist Professor Intensive Care									
Hoogveen	Member, nephrologist	Member of Guideline Committee of Dutch Federation of Nephrology	None	None	Member of Guideline Committee of Dutch Society for Nephrology	Grant from the Dutch Kidney Foundation to study effect of fish oil on kidney function in post-MI patients	None	None	None	Yes
Sijkens	Member, nephrologist	None	None	None	None	None	None	None	None	Yes
Van den Meiracker	Member, internist vascular medicine	None	None	None	None	None	None	None	None	Yes
Cobbaert	Member, physician clinical chemistry	Head of clinical chemistry department in Leiden LUMC. Tutor for post-academic training of clinical chemists, coordinator/host for the Leiden region Member of several working groups within the Dutch Society for Clinical Chemistry and member of several international working groups for clinical chemistry	None	None	Member of several working groups within the Dutch Society for Clinical Chemistry and member of several international working groups for clinical chemistry	None	None	None	None	Yes
Wikkeling	Member, vascular surgeon	None	None	None	None	None	None	None	None	Yes
Vainas	Member, vascular surgeon	None	None	None	None	None	None	None	None	Yes
Kooiman	Member, research physician	Resident in department of gynaecology & obstetrics	None	None	None	None	None	None	None	Yes
Burger	Advisor,	None	None	None	None	None	None	None	None	Yes

	Knowledge Institute of Medical Specialists								
Mostovaya	Advisor, Knowledge Institute of Medical Specialists	None	None	None	None	None	None	None	Yes
Advisory Board									
Prantl	Member, policy maker, Dutch Society of Kidney Patients	None	None	None	None	None	None	None	Yes
Hubbers	Member, patient's representative, Dutch Society of Kidney Patients	None	None	None	None	None	None	None	Yes
Mazel	Member, urologist	None	None	None	None	None	None	None	Yes
Van den Wijngaard	Member, resident clinical chemistry	Reviewer for several journals (such as American Journal of Physiology)	None	None	None	None	None	None	Yes
Demir	Member, physician clinical chemistry	None	None	None	None	None	None	None	Yes

Input of patient's perspective

Patients' perspective was represented, firstly by membership and involvement in the advisory board of a policy maker and a patients' representative from the Dutch Kidney Patient Association. Furthermore, an online survey was organized by the Dutch Kidney Patient Association about the subject matter of the guideline. A summary of the results of this survey has been discussed during a working group meeting at the beginning of the guideline development process. Subjects that were deemed relevant by patients were included in the outline of the guideline. The concept guideline has also been submitted for feedback during the comment process to the Dutch Patient and Consumer Federation, who have reported their feedback through the Dutch Kidney Patient Association.

Implementation

In the different phases of guideline development, the implementation of the guideline and the practical enforceability of the guideline were taken into account. The factors that could facilitate or hinder the introduction of the guideline in clinical practice have been explicitly considered. The implementation plan can be found with the Related Products. Furthermore, quality indicators were developed to enhance the implementation of the guideline. The indicators can also be found with the Related Products.

Methodology

AGREE

This guideline has been developed conforming to the requirements of the report of Guidelines for Medical Specialists 2.0; the advisory committee of the Quality Counsel (www.kwaliteitskoepel.nl). This report is based on the AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II) (www.agreetrust.org), a broadly accepted instrument in the international community and on the national quality standards for guidelines: Guidelines for guidelines (www.zorginstituutnederland.nl).

Identification of subject matter

During the initial phase of the guideline development, the chairman, working group and the advisor inventory the relevant subject matter for the guideline. Furthermore, an Invitational Conference was organized, where additional relevant subjects were suggested by the Dutch Kidney Patient Association, Dutch Society for Emergency Physicians, and Dutch Society for Urology. A report of this meeting can be found in Related Products.

Clinical questions and outcomes

During the initial phase of guideline development, the chairman, working group and advisor identified relevant subject matter for the guideline. Furthermore, input was acquired for the outline of the guideline during an Invitational Conference. The working group then formulated definitive clinical questions and defined relevant outcome measures (both beneficial and harmful effects). The working group rated the outcome measures as critical, important and not important. Furthermore, where applicable, the working group defined relevant clinical differences.

Strategy for search and selection of literature

For the separate clinical questions, specific search terms were formulated and published scientific articles were sought after in (several) electronic databases. Furthermore, studies were looked for by cross-referencing other included studies. The studies with potentially the highest quality of research were looked for first. The working group members selected literature in pairs (independently of each other) based on title and abstract. A second selection was performed based on full text. The databases search terms and selection criteria are described in the modules containing the clinical questions.

Quality assessment of individual studies

Individual studies were systematically assessed, based on methodological quality criteria that were determined prior to the search, so that risk of bias could be estimated. This is described in the risk of bias tables.

Summary of literature

The relevant research findings of all selected articles are shown in evidence tables. The most important findings in literature are described in literature summaries. When there were enough similarities between studies, the study data were pooled.

Grading the strength of scientific evidence

A) For intervention questions

The strength of the conclusions of the scientific publications was determined using the GRADE-method. GRADE stands for Grading Recommendations Assessment, Development and Evaluation (see <http://www.gradeworkinggroup.org/>) (Atkins, 2004).

GRADE defines four gradations for the quality of scientific evidence: high, moderate, low or very low. These gradations provide information about the amount of certainty about the literature conclusions. (<http://www.guidelinedevelopment.org/handbook/>).

Code	Quality of Evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect. <ul style="list-style-type: none">▶ Several high-quality studies with consistent results▶ In special cases: one large, high-quality multi-centre trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. <ul style="list-style-type: none">▶ One high-quality study▶ Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. <ul style="list-style-type: none">▶ One or more studies with severe limitations
D	Very Low	Any estimate of effect is very uncertain. <ul style="list-style-type: none">▶ Expert opinion▶ No direct research evidence▶ One or more studies with very severe limitations

B) *For diagnostic, etiological, prognostic or adverse effect questions, the GRADE-methodology cannot (yet) be applied. The quality of evidence of the conclusion is determined by the EBRO method (van Everdingen, 2004)*

Formulating conclusion

For diagnostic, etiological, prognostic or adverse effect questions, the evidence was summarized in one or more conclusions, and the level of the most relevant evidence was reported. For intervention questions, the conclusion was drawn based on the body of evidence (not one or several articles). The working groups weighed the beneficial and harmful effects of the intervention.

Considerations

Aspects such as expertise of working group members, patient preferences, costs, availability of facilities, and organization of healthcare aspects are important to consider when formulating a recommendation. These aspects were discussed in the paragraph Considerations.

Formulating recommendations

The recommendation answers the clinical question and was based on the available scientific evidence and the most relevant considerations.

Constraints (organization of healthcare)

During the development of the outline of the guideline and the rest of the guideline development process, the organization of healthcare was explicitly taken into account. Constraints that were relevant for certain clinical questions were discussed in the Consideration paragraphs of those clinical questions. The comprehensive and additional aspects of the organization of healthcare were discussed in a separate chapter.

Development of quality indicators

Internal (meant for use by scientific society or its members) quality indicators are developed simultaneously with the guideline. Furthermore, existing indicators on this subject were critically appraised; and the working group produces an advice about such indicators. Additional information on the development of quality indicators is available by contacting the Knowledge Institute for Medical Specialists. (secretariaat@kennisinstituut.nl).

Knowledge Gaps

During the development of the guideline, a systematic literature search was performed the results of which help to answer the clinical questions. For each clinical question the working group determined if additional scientific research on this subject was desirable. An overview of recommendations for further research is available in the appendix Knowledge Gaps.

Comment- and authorisation phase

The concept guideline was subjected to commentaries by the involved scientific societies. The commentaries were collected and discussed with the working group. The feedback was used to improve the guideline; afterwards the working group made the

guideline definitive. The final version of the guideline was offered for authorization to the involved scientific societies, and was authorized.

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Chapter 3 PC-AKI: Definitions, Terminology & Clinical course

Post-Contrast-AKI: Terminology and definitions

Because of the recent developments there is confusion about terminology. Terms as post-contrast acute kidney injury, contrast-associated acute kidney injury, and contrast-induced acute kidney injury or contrast-induced nephropathy are incorrectly used interchangeably.

Therefore, the working group suggests adaptation of the suggestion of the American College of Radiology (ACR) Committee on Drugs and Contrast Media, put forward in their Manual on Contrast Media for more uniformity (ACR Manual, 2017).

Post Contrast Acute Kidney Injury (PC-AKI) is a general term used to describe a sudden deterioration in renal function that occurs within 48 hours following the intravascular administration of iodine-containing contrast medium. PC-AKI may occur regardless of whether the contrast medium was the cause of the deterioration. PC-AKI is a *correlative* diagnosis.

Contrast-Induced Acute Kidney Injury (CI-AKI) or Contrast-Induced Nephropathy (CIN) is a specific term used to describe a sudden deterioration in kidney function that is caused by the intravascular administration of iodine-containing contrast medium; therefore, CI-AKI/CIN is a subgroup of PC-AKI. CI-AKI/CIN is a *causative* diagnosis.

The ACR acknowledges that very few published studies have a suitable control group to permit the differentiation of CI-AKI/CIN from PC-AKI. Therefore, the incidence of PC-AKI reported in clinical studies and the incidence of PC-AKI observed in clinical practice likely includes a combination of CI-AKI/CIN (i.e., AKI caused by contrast medium administration) and AKI unrelated to contrast medium administration (i.e., AKI coincident to, but not caused by contrast medium administration). It should be clear that these terms are not interchangeable.

PC-AKI is not synonymous with CI-AKI / CIN (ACR Manual, 2017).

Definitions and their history

In critical care, acute renal failure is a complex disorder with a wide variety of aetiologies and possible risk factors. Despite improved knowledge from animal studies, there was a lack of uniform definition of this disorder. This challenge has been taken on by multiple groups in the Nephrology community, among them the Acute Dialysis Quality Initiative (ADQI) (Bellomo, 2004) and the Kidney Disease: Improving Global Outcome (KDIGO) (Levey, 2005) groups.

During the first meeting of the Acute Kidney Injury Network (AKIN), a network of experts in Critical Care and Nephrology, the term Acute Kidney Injury (AKI) was suggested as the preferred uniform terminology for acute renal failure. This was diagnosed as “an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine (sCr) of ≥ 0.3 mg/dl (≥ 26.4 μ mol/l), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine

output (documented oliguria of less than 0.5 ml/kg per hour for more than six hours)” (Mehta, 2007). In clinical practice a 50% increase in sCr >3 and <7 days can be used. This definition is thus applicable to all forms of AKI and is not specific for contrast-induced AKI. This was subsequently adapted into the KDIGO Practice Guidelines in 2012. According to this guideline, AKI can be subdivided in 3 stages (see Table 3.1) according to criteria adapted from the RIFLE (Risk, Injury, Failure, Loss, End Stage) criteria (Drüeke, 2012):

Table 3.1: KDIGO staging of AKI

<i>Stage</i>	<i>Serum creatinine criteria</i>	<i>Urine output criteria</i>
1	sCr increase ≥ 0.3 mg/dl (≥ 26.5 $\mu\text{mol/l}$), or sCr increase ≥ 1.5 to 1.9 x baseline	<0.5 ml/kg/h for 6 to 12h
2	sCr increase >2.0 to 2.9x baseline	<0.5 ml/kg/h for ≥ 12 h
3	sCr ≥ 4.0 mg/dl (≥ 354 $\mu\text{mol/l}$) sCr increase >3.0 x baseline or initiation of renal replacement therapy	<0.3 ml/kg/h for ≥ 24 h Anuria for ≥ 12 h

Of note: 1 mg/dl serum Creatinine equals 88,4 $\mu\text{mol/l}$.

In the mid 1990s, the Contrast Media Safety Committee (CMSC) of the European Society of Urogenital Radiology (ESUR) was founded, a group of experienced CM researchers from Radiology, that was set out to make expert-based guidelines. The most frequently used definition of Contrast-Induced Nephropathy (CIN), is from their first renal guideline: CIN refers to a condition in which an impairment in renal function (an increase in serum creatinine by more than 25% or 44 $\mu\text{mol/l}$ (or 0.5 mg/dl) occurs within 3 days following the intravascular administration of a contrast medium in the absence of an alternative aetiology (Morcos, 1999). More stringent definitions have been used in older studies, e.g. using a sCr increase >1 mg/dl [88 $\mu\text{mol/l}$] or 50% (Aspelin, 2003). However, these have not really caught on a wide scale in more recent times.

This resulted in another confusion that has still not been adequately resolved by a consensus definition (Endre, 2010; Meinel, 2014). It has been shown in multiple studies that the percentage of patients with CIN is largely dependent on the definition used (Jabara, 2009; Pyxaras, 2015; Weisbord, 2008).

A relative increase in sCr of >25% has been the most sensitive indicator, whereas absolute value definitions led to lower rates of CIN. In some studies relative increases in sCr were found to overestimate CIN and absolute values were preferable (Budano, 2011), while in other studies relative definitions were stronger associated with prognostic relevance in coronary angiography (Pyxaras, 2015). A recent study showed that the combination of an absolute sCr increase >0.3 mg/dl [25 mol/l] or a relative sCr increase >50% might be the most optimal definition (Parsh, 2016).

However, these figures of CIN are usually not well related to hard clinical endpoints such as (short-term) renal replacement therapy dependency, morbidity or mortality. Some studies in critically ill populations have shown a benefit of the AKIN-definition of post-contrast AKI on ICU mortality (Lakhal, 2011).

Already in 2006, a CIN Consensus Working Panel formed by GE Healthcare with experts from various disciplines indicated that the ADQI-RIFLE criteria may be important in the future for defining PC-AKI (McCullough, 2006). Many researchers in radiology and cardiology are now moving towards adaptation of the AKIN criteria as the standard for

studies on contrast-induced AKI (Garfinkle, 2015). Therefore, we suggest, similar to the European Renal Best Practice (ERBP) working group in their comment on the KDIGO 2012 practice guidelines on AKI, that there seems to be no good reason why the definition of PC-AKI (or CI-AKI) should be different from the general definition of other forms of AKI (Fliser, 2012; Kooiman, 2016; Thomas, 2015), even though CI-AKI /CIN and PC-AKI are not completely interchangeable.

Clinical Course and Incidence

PC-AKI is an iatrogenic renal injury that follows intravascular administration of CM in susceptible individuals. (Rear, 2016). The proliferation in imaging methods and interventions involving administration of intravascular CM has significantly increased the number of patients exposed to CM and consequently the number of patients at risk for PC-AKI.

Discrimination between different causes of AKI in patients subjected to iodine-containing CM administration is difficult. In most of cases PC-AKI is mild and reversible with returning of renal function to baseline or near baseline values within 1-3 weeks (Mehran, 2006; Guitterez, 2002). As common for all forms of AKI, the occurrence of PC-AKI has shown to be a marker for increased short- and long-term morbidity and/or mortality and prolonged hospital stay (Gupta; 2005; Gruberg, 2000; Mitchell, 2015; Kooiman, 2015; Rihal, 2002; Rudnick, 2008).

Various studies suggest that the route of administration of iodine-containing CM (intra-arterial versus intravenous) and the type of procedure (i.e. catheter-based angiography versus CT imaging) can have a substantial impact on the incidence of PC-AKI. (Dong, 2012) However, in four retrospective studies the risk of PC-AKI and clinical course did not differ in patients who underwent both intra-arterial and intravenous contrast administration within a restricted time span. (Karlsberg, 2011; Kooiman, 2013; Tong, 2016; McDonald, 2016)

The cause of AKI following catheter angiography is in many instances multifactorial and may erroneously be diagnosed as PC-AKI. (Keeley, 1998) For instance, catheter-based procedures as compared to contrast-enhanced computed tomography (CE-CT) may be complicated by haemodynamic instability leading to post-interventional AKI, which may be misinterpreted as contrast-induced nephropathy (Bruce, 2009; Newhouse, 2008). In addition, cholesterol emboli, aortic plaque fragments and thrombi may be physically dislodged during catheter manipulation, leading to micro-embolization of the kidney and post-procedural impairment of kidney function (Wichmann, 2015).

Two recent meta-analyses of 40 and 42 studies in about 19,000 patients undergoing CE-CT revealed a weighted pooled incidence of PC-AKI of 6.4% (95%CI 5.0-8.1%) and 5.0% (95%CI 3.8-6.5%). (Kooiman, 2012; Moos, 2013) In the meta-analysis of Moos et al. chronic kidney disease (CKD), diabetes, malignancy, age >65 years and use of non-steroidal anti-inflammatory drugs (NSAID's) and in the meta-analysis of Kooiman et al. CKD and diabetes were associated with an increased risk. In about 1% of all patients (follow-up one week to two months after CE-CT) the renal function decline persisted, but the weighted pooled incidence of renal replacement therapy was as low as 0.06%. (Kooiman, 2012) The authors of this meta-analysis conclude that, given the low

incidence of PC-AKI in general and the rare occurrence of a persistent decline in renal function, CM in the setting of a CT can be safely administered to the vast majority of patients. However, as emphasized by the authors, since in most of the studies pre- and post-hydration was performed in patients at high risk for PC-AKI, the results are not generalizable to high risk patients without pre- and/or post-hydration.

Meta-analyses of non-randomized studies comparing outcomes of patients who underwent CT with and without iodine-containing CM bear the risk of selection bias. Recently, propensity score matching has been introduced to the field of PC-AKI. Propensity score matching is a statistical method used in observational studies with low incidence of outcome under study that takes measured confounding into account (Rosenbaum, 1984). McDonald JS, et al. performed a propensity score-based matched study in over 12,500 patients, and did not find an increased risk of PC-AKI, acute dialysis, or 30-day mortality in patients who underwent CE-CT versus those who did not. (McDonald, 2014) Using propensity-score based matching in over 17,500 patients Davenport et al. also did not observe an increased risk for AKI in patients with normal renal function after intravenous CM administration for CT, but they reported an increased incidence of AKI in patients with an eGFR <30 ml/min/1.73m² (Davenport, 2013). These findings suggest that the incidence of CI-AKI in patients undergoing contrast-enhanced CT with intravenous iodine-containing CM administration is likely to be substantially lower than previously estimated. However, the clinical course of AKI after CE-CT may not always be as favourable as evidenced by the abovementioned studies. In a prospective observational study concerning 633 emergency department patients undergoing CE-CT without pre-hydration PC-AKI occurred in 70 patients (11%), with persistent renal failure at one-year follow-up in 11 of these patients. (Mitchell, 2015) It should be emphasized that these patients had an emergent indication for CE-CT and might therefore have other risk factors (such as haemodynamic instability) for AKI.

In 5244 patients with ST-Elevation Myocardial Infarction (STEMI) treated with PCI the incidence of PC-AKI for patients with a baseline eGFR of >90 , 60-90, 30-59 and <30 ml/min/1.73 m² was 2.1%, 3.4%, 7.3% and 1.8%, respectively, underlining pre-existent CKD as a risk factor of PC-AKI. (Vavalle, 2016) The relatively low incidence of PC-AKI in the group of patients with an eGFR <30 ml/min/1.73 m² may be related to the small number of patients (n=89) present in this subgroup. Impaired renal function at presentation and development of PC-AKI were highly associated with worse clinical outcome, including death. A meta-analysis of 39 observational studies including 139,603 participants that investigated cardiovascular outcomes in those with PC-AKI demonstrated an increased risk of mortality, cardiovascular events, renal failure and prolonged hospitalization. (James, 2013) Baseline characteristics that simultaneously predispose to both mortality and PC-AKI were regarded as confounders. The reported incidence of end stage renal disease ranged from 0% to 0.2% in those without PC-AKI and from 0.2% to 4.5% in those with PC-AKI. In a more recent study consisting of 92,317 PCI procedures performed in 90,383 patients the incidence of PC-AKI was 2.3% and of renal replacement therapy 0.3%. (Kooiman, 2015) As expected patients developing PC-AKI had a greater burden of co-morbidity at baseline and was more likely to have adverse in-hospital outcomes. Using propensity-score based matching (1,371 patients with PC-AKI versus 5,484 patients without PC-AKI) in-hospital major adverse clinical outcomes (in-hospital mortality, cardiogenic shock, heart failure, stroke, bleeding and new requirement for dialysis post-PCI) were considerably and significantly higher in AKI

versus non-AKI patients and nearly one-third of the in-hospital mortality risk post PCI appeared to be attributable to AKI, demonstrating its clinical importance. (Kooiman, 2015)

In conclusion, the incidence of PC-AKI after intravenous or intra-arterial iodine-containing CM administration in general is low and directly related to the presence and severity of CKD prior to contrast administration and concomitant co-morbidities as demonstrated by propensity-score based matching analyses. The decline in renal function is mostly transient, but in rare instances renal replacement therapy is required with reported incidences of 0.06% after CE-CT and 0.2% to 0.6% post PCI. PC-AKI is a marker of poor outcomes, including increased short- and long-term mortality. Whether there is a causal relation between PC-AKI and poor outcomes remains unclear. However, reducing the incidence of PC-AKI in high risk patients (such as those undergoing emergent PCI, or with an eGFR <30 ml/min/1.73m²) by optimal risk stratification and preventive measures, remains a major goal in clinical practice.

Terminology of the routes of CM administration

A difference has been made in guidelines between intravenous and intra-arterial CM administration. **Intravenous CM administration** implies that the CM will reach the renal arteries after dilution by circulation through the right heart and pulmonary or a systemic vascular bed. The same applies to **intra-arterial CM administration with second pass renal exposure** administrations, that is: administration distal to the renal arteries and to CM administration after selective catheterisation of the suprarenal aortic side branches, e.g. injections via catheters in the carotid, subclavian, brachial, coronary and mesenteric arteries, except for the minimal back flow into the aorta of which only 20% will reach the renal arteries directly. In **intra-arterial CM administration with first pass renal exposure** the CM will reach the renal arteries without being diluted by a capillary bed, as is the case when the CM is injected via catheters in the left ventricle, thoracic aorta, suprarenal abdominal aorta, or selectively in the renal arteries.

Since this guideline only uses a single cut-off value of eGFR <30 ml/min/1.73m² for preventive IV hydration, the distinction between IV or IA iodinated CM is largely theoretical and has no prevention consequences. Therefore, both IV and IA iodinated CM administration will be referred to by the general term **intravascular CM administration**.

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Chapter 4 Risk Stratification and Risk Stratification Tools

Clinical question

How to identify patients at high risk for post-contrast acute kidney injury (PC-AKI) who receive intravascular iodine-containing contrast medium?

Sub questions

- 4.1.1 What is the risk for PC-AKI in patients receiving iodine-containing contrast administration compared to patients receiving no contrast administration?
- 4.1.2. Which risk factors for PC-AKI can be identified in patients scheduled for an imaging procedure with iodine-containing CM?
- 4.2 How should a history of kidney transplantation be taken into account when assessing a patient for PC-AKI risk?
- 4.3 How should a solitary kidney be taken into account when assessing a patient for PC-AKI risk?
- 4.4 How should the osmolality of iodine-containing contrast medium be taken into account when assessing PC-AKI risk?
- 4.5 How to use questionnaires and prediction tools to estimate risk of PC-AKI?

Introduction

Post-contrast acute kidney injury (PC-AKI) is acute kidney injury after exposure to iodine-containing contrast medium. The Dutch Centraal Begeleidings Orgaan (CBO) 2007 guideline defined CIN (PC-AKI in this guideline) as an increase of serum creatinine of >25% or >44 μ mol/L within 3 to 5 days after exposure to iodine-containing contrast medium. In the CBO 2007 guideline the prediction of the risk for PC-AKI and dialysis was based on the Mehran risk-score. A risk-score of >1% for dialysis treatment was considered "high risk of PC-AKI" for which pre-hydration and post-hydration with 1L NaCl 0.9% are indicated. The CBO 2007 guideline has been implemented in the Safety-Management-System of the Hospitals in The Netherlands.

Recent studies show a much lower risk of PC-AKI and need for dialysis treatment after exposure to iodine-containing contrast media. Most likely, incidence and severity of PC-AKI have been overestimated by previous uncontrolled studies. All instances of AKI after iodine-containing contrast media administration were ascribed to PC-AKI, even though there are many other causes of AKI. Therefore, we explored from recent studies the risk of PC-AKI in patients scheduled for intravenous or intra-arterial iodine-containing CM-enhanced procedures.

Optimal Nephrology Care

In addition to prevention of PC-AKI, optimal nephrology care is important to prevent AKI in patients with impaired renal function. Currently, end stage renal disease (ESRD) is most often caused by atherosclerotic vascular disease, hypertension and type 2 diabetes. The goal in patients with chronic kidney disease (CKD) stage 3 to 5 (non-dialysis) is to slow down deterioration of renal function and prevent or postpone cardiovascular morbidity and mortality. According to the guideline Care of the Patient with Chronic Renal Damage (2009) of the Dutch Federation of Nephrology (NFN), the following advices for optimal nephrology care are relevant for the present guideline:

avoid nephrotoxic medications, avoid dehydration and hypovolemia, and refer patients with eGFR <30 ml/min/1.73m² to a nephrologist.

Search and selection of literature

To answer our clinical question a systematic literature analysis was performed for the sub questions 4.1.2-4.5. We formulated the following research questions and accompanying PICOs:

Which risk factors have the best value in identification of patients with increased risk of PC-AKI?

PICO 1

P (patient category) adult (≥18 years) patients receiving intravascular contrast
I (intervention) risk factors: patient-related, treatment-related, contrast administration related
C (comparison) absence of these risk factors
O (outcome) PC-AKI, complications of PC-AKI (hospitalization, start of dialysis, mortality)

PICO 2

P (patient category) adult (≥18 years) patients receiving intravascular contrast;
I (intervention) iodine-containing contrast medium administration;
C (comparison) no iodine-containing contrast medium administration;
O (outcome) PC-AKI, complications of PC-AKI (hospitalization, start of dialysis, mortality).

PICO 3

P (patient category) adult (≥18 years) patients receiving intravascular contrast;
I (intervention) iodine-containing contrast medium administration with hydration;
C (comparison) iodine-containing contrast medium administration with no hydration;
O (outcome) PC-AKI, complications of PC-AKI (hospitalization, start of dialysis, mortality).

PICO 4

P (patient category) adult (≥18 years) patients receiving intravascular contrast;
I (intervention) administration with iso-osmolar iodine-containing contrast medium;
C (comparison) administration with low osmolar iodine-containing contrast medium;
O (outcome) PC-AKI, complications of PC-AKI (hospitalization, start of dialysis, mortality).

Which clinical tools or questionnaires have the best diagnostic value in identification of patients with increased risk of PC-AKI?

PICO 5

P (patient category) adult (≥18 years) patients receiving intravascular iodine-containing contrast medium;

I (intervention)	questionnaires or other clinical tools to estimate risk of PC-AKI;
C (comparison)	other questionnaires or other clinical tools to estimate risk of PC-AKI;
Reference test	development of PC-AKI after intravascular contrast administration;
O (outcome)	sensitivity, specificity, area under curve (AUC), validity, reliability.

Relevant outcome measures

The working group considered sensitivity, specificity, AUC, validity, reliability critical outcome measures for the decision making process. The working group defined PC-AKI as described in the chapter Terminology.

Search and select (method)

A separate search strategy was developed for the first four research sub questions (PICO 1 – 4) and the fifth sub question (PICO 5).

For the sub questions 4.1 – 4.4, the databases Medline (OVID), Embase and the Cochrane Library were searched from 1st of January 2000 up to 19th of August 2015 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). This search was updated on April 14th 2017. A total of 1058 studies were found. The initial literature search procured 868 hits and the update retrieved an additional 190 studies.

Studies were selected based on the following criteria:

- adult patients who underwent radiological examination using intravascular iodine-containing contrast media (including radiological examination during percutaneous angiography);
- potential risk factors related either to patient characteristics and/or treatment characteristics and/or iodine-containing contrast medium characteristics were studied in how they influenced the risk of PC-AKI;
- risk factors were corrected for confounders in multivariable models;
- at least one of the outcome measures was described: PC-AKI, complications of PC-AKI (hospitalization, start of dialysis, mortality).

For sub question 4.1.1, the working group selected the studies in which the risk of PC-AKI was compared for patients receiving intravascular contrast to patients receiving no intravascular contrast.

For the fifth sub question, the databases Medline (OVID), Embase and the Cochrane Library were searched from 1st of January 1995 up to 24th of September 2015 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). This search was updated on April 14th, 2017. A total of 393 studies were found. The initial literature search procured 311 hits and the update retrieved an additional 82 studies.

Studies were selected based on the following criteria:

- adult patients who underwent radiological examination using intravascular iodine-containing contrast media (including radiological examination during percutaneous angiography);

- a measurement instrument that has been validated and estimates the risk of PC-AKI;
- if patients had to fill in the measurement instrument, we applied an additional criterion that the instrument had to be validated in Dutch and available in the Netherlands;
- at least one of the outcome measures was described: sensitivity, specificity, AUC, validity, reliability.

PICO 1

Based on title and abstract a total of 385 studies were initially selected (325 in the initial search and 60 in the updated search). After examination of full text a total of 331 studies were excluded and 54 studies definitely included in the literature summary.

PICO 2-4

Based on title and abstract a total of 210 studies were selected. After examination of full text a total of 186 studies were excluded and 24 studies definitely included in the literature summary. A total of two studies were added after the update of the search: one regards patients with a history of kidney transplantation and one regard patients with a solitary kidney.

PICO 5

Based on title and abstract a total of 91 studies were selected (56 in the initial search and 35 in the updated search). One more study was added through cross-referencing. After examination of full text a total of 73 studies were excluded and 19 studies definitely included in the literature summary.

Results

PICO 1

54 studies were included in the literature analysis, the most important study characteristics and results were included in the evidence tables. The evidence tables and assessment of individual study quality are included.

PICO 2-4

26 studies were included in the literature analysis, the most important study characteristics and results were included in the evidence tables. The evidence tables and assessment of individual study quality are included.

PICO 5

19 studies were included in the literature analysis, the most important study characteristics and results were included in the evidence tables. The evidence tables and assessment of individual study quality are included.

Summary of literature

4.1.1 Studies comparing iodine-containing contrast administration to no contrast administration

Description of studies

There are no RCTs that compared risk of AKI after a radiological procedure with or without iodine-containing CM. Moreover, most identified risk factors for PC-AKI are also

risk factors for AKI. As a consequence, we can only summarize risk factors for PC-AKI from observational studies. Since these risk factors cannot reliably discriminate between risk of AKI or PC-AKI, we could not use these specific risk factors for the present guideline to identify patients who are at increased risk for PC-AKI.

Study results

There are no prospective randomized controlled trials (RCTs) that compared the risk of AKI in patients undergoing CT scans with or without low osmolar (LO) CM. Three retrospective observational studies compared the incidence of AKI in patients who underwent CT-scans either with or without intravenous contrast administration (Bruce, 2009; McDonald RJ, 2013; Davenport 2013a). Bruce, 2009 matched contrast and non-contrast patients by eGFR, while McDonald and Davenport used Propensity Score matching.

Both Bruce (2009) and McDonald (2013) reported in respectively 11,588 and 53,439 patients that risk of post CT-scan AKI was similar in patients who underwent CT-scans with intravenous contrast and those who underwent CT-scans without intravenous contrast.

Bruce (2009) reported that 525/5,328 (10%) of patients receiving iohexol CM developed PC-AKI compared to 45/462 (10%) patients receiving iodixanol CM and 658/7,484 (9%) patients receiving no CM ($p>0.05$).

McDonald (2013) reported that AKI risk was not significantly different between contrast and non-contrast groups in any risk subgroup after propensity score (PS) matching by using reported risk factors of CIN (low risk: odds ratio [OR], 0.93; 95%CI: 0.76, 1.13; $p=0.47$; medium risk: OR, 0.97; 95% CI: 0.81, 1.16; $p=0.76$; high risk: OR, 0.91; 95% CI: 0.66, 1.24; $p=0.58$). Counterfactual analysis revealed no significant difference in AKI incidence between enhanced and unenhanced CT scans in the same patient (McNemar test: $\chi(2) = 0.63$, $p=0.43$) (OR = 0.92; 95% CI: 0.75, 1.13; $p=0.46$).

In contrast, Davenport (2013) showed in a 10-year 1:1 propensity score-matched retrospective study, including 17,652 patients with a stable kidney function, that inpatients with an eGFR <30 ml/min/1.73m² had a 3-fold increased risk of PC-AKI compared to patients without LOCM enhanced CT (OR 2.96 (95%CI: 1.22-7.17) (Davenport 2013a), with a trend toward significance in patients with an eGFR 30-44 ml/min/1.73m². IV LOCM did not appear to be associated with PC-AKI in patients with an eGFR >45 ml/min/1.73m².

4.1.2 Risk Factor Analysis (Which risk factors for PC-AKI can be identified in patients scheduled for an imaging procedure with iodine-containing CM?)

Description of studies

A total of 54 observational studies that examined the determinants of PC-AKI risk in a multivariable model were included in this literature analysis.

Ten studies examined PC-AKI risk in patients undergoing Computed Tomography scans with intravenous iodine-containing contrast. The study populations of these studies ranged from 189 to 17,672 patients. The multivariable models contained 4 to 14

parameters. (Balemans, 2012; Davenport, 2013a; Diogo, 2014; Ho, 2015; Kwasa, 2014; Matsushima, 2011; Moos, 2014; Selistre, 2015; Sonhay, 2015; Yazici, 2016)

Forty-four studies examined PC-AKI risk in patients undergoing coronary angiography (CAG) and/or percutaneous coronary intervention (PCI) with intra-arterial iodine-containing contrast medium. The study populations of these studies ranged from 102 to 8357. The multivariable models contained 2 to 12 parameters. (Aguar-Souto, 2010; Barbieri, 2014; Chong, 2009; Chong, 2010; Chong, 2010_1; Chong, 2015; Cicek, 2015; Cirit, 2006; Dangas, 2005; Ding, 2013; Diogo, 2010; Ebisawa, 2016; Farhan, 2016; Fu, 2012; Gao, 2014; Guo, 2015; Gurm, 2013; Ivanes, 2014; Kiski, 2010; Kolte, 2016; Lin, 2014; Liu, 2012; Liu, 2012_1; Lucreziotti, 2014; Mager, 2011; Maioli, 2011; Medalion, 2010; Mehran, 2004; Nikolsky, 2005; Ozcan, 2015; Ozturk, 2016; Pakfertat, 2010; Ranucci, 2013; Sahin, 2014; Saito, 2015; Taniguchi, 2013; Toprak, 2006; Toprak, 2006_1; Toprak, 2007; Uçar, 2014; Watanabe, 2016; Zhu, 2016; Zuo, 2016)

Study results

1. PC-AKI risk for CT with: intravenous iodine-containing contrast administration
As shown in tables 4.1, 4.2 and 4.3 (Appendix) the following risk factors for the development of PC-AKI were identified in patients who underwent a CT-scan and intravenous iodine-containing contrast medium administration:

Patient factors:

- chronic heart failure (risk factor in 5 out of 7 studies);
- diabetes (risk factor in 5 out of 7 studies);
- older age (risk factor in 3 out of 7 studies);
- sex (male) (risk factor in 2 out of 6 studies);
- chronic kidney disease (risk factor in 2 out of 4 studies);
- inflammation (clinical sepsis or high C-reactive protein) (risk factor in 1 study);
- medication: use of hydrochlorothiazide, diuretics or concurrent use of 4 nephrotoxic agents (all reported in 1 study);
- hypotension (risk factor in 1 study);
- Injury Severity Score in trauma CT (risk factor in 1 study);
- African American race (risk factor in 1 study);

Laboratory parameters:

- risk of PC-AKI is increased for patients if $eGFR < 60 \text{ mL/min/1.73m}^2$ (risk factor in 3 out of 3 studies);
- risk of PC-AKI is inversely associated with kidney function (risk factor in 1 out of 2 studies);
- haemoglobin level ($< 9.3 \text{ g/dL}$) (risk factor in 1 out of 3 studies)

Treatment-related parameters:

- emergency CT-scan (decrease of risk in 1 study);
- length of hospital stay (risk factor in 1 study);
- blood transfusion (risk factor in 1 study).

2. PC-AKI risk for CAG and PCI with intra-arterial iodine-containing contrast administration

As shown in tables 4.4, 4.5 and 4.6 (Appendix) the following risk factors for the development of PC-AKI were identified in patients who underwent a CAG and/or PCI and intra-arterial contrast administration:

Patient factors:

- chronic kidney disease (risk factor in 4 out of 4 studies);
- multivessel coronary artery disease (risk factor in 3 out of 3 studies).
- older age (risk factor in 16 out of 22 studies);
- history of heart failure (risk factor in 12 out of 19 studies);
- history of diabetes (risk factor in 16 out of 23 studies);
- body mass index (BMI), either overweight ($>25 \text{ kg/m}^2$, risk factor in 2 out of 3 studies) or underweight ($<18.5 \text{ kg/m}^2$, risk factor in 1 out of 3 studies);
- peripheral vascular disease (risk factor in 2 out of 3 studies);
- metabolic syndrome (risk factor in 2 out of 3 studies);
- sex (women) (risk factor in 6 out of 13 studies);
- hypertension (risk factor in 2 out of 13 studies) or hypotension at admission (risk factor in 2 out of 13 studies);
- risk score (SYNTAX) (risk factor in 1 study);
- medication: statins (decrease of risk in 1 study), diuretics, calcium antagonists, insulin, angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARB) (no consistent risk factors);
- ST-elevation myocardial infarction (risk factor in 1 study)
- cardiogenic shock (risk factor in 1 study);
- pulmonary oedema at presentation (risk factor in 1 study);

Laboratory parameters:

- eGFR (lower) (risk factor in 18 out of 27 studies);
- serum creatinine (risk factor in 6 out of 9 studies)
- low haemoglobin / anaemia (risk factor in 10 out of 15 studies);
- low albumin (risk factor in 3 out of 3 studies)
- hyperuricemia (risk factor based on meta-analysis);
- proteinuria (risk factor in 2 out of 3 studies);
- cysteine-C (risk factor in 2 out of 2 studies)
- hypercholesterolemia (risk factor in 1 out of 2 studies);
- myoglobin (risk factor in 1 study);
- serum glucose (risk factor in 1 study)
- increased C-reactive protein (risk factor in 1 study);
- serum ferritin (risk factor in 1 study);

Treatment-related parameters:

- intra-aortic balloon pump (risk factor in 7 out of 7 studies);
- contrast volume: sometimes reported as ratio between administered contrast volume and eGFR, ratio between contrast volume and body surface area or maximal estimated contrast dose (risk factor in 16 out of 22 studies);
- emergency PCI (risk factor in 2 out of 3 studies);
- surgical procedure on the same day (risk factor in 1 study);

- duration of cardiac bypass (CABG) (risk factor in 1 study);
- nadir haematocrit during CABG (risk factor in 1 study);
- prehydration with saline or non-normal saline hydration (both risk factor in 1 study);
- multivessel intervention (risk factor in 1 study);
- periprocedural hypotension (risk factor in 1 study).

4.2 How should a history of kidney transplantation be taken into account when assessing a patient for PC-AKI risk?

Description of studies

Only a limited number of studies reported about kidney transplant recipients that received intravascular iodine-containing contrast. We found no prospective studies of PC-AKI in kidney transplant recipients. We included three retrospective studies with a limited number of patients. No studies were found about kidney transplant recipients with more advanced CKD (eGFR <45 ml/min/1.73m²) and risk of PC-AKI.

Study results

Haider, 2015 conducted a retrospective study to evaluate the incidence of PC-AKI in kidney transplant recipients. Patients received intravascular iodine-containing contrast for a CT scan, pulmonary angiogram, or cardiac catheterization. PC-AKI was defined as a rise in serum creatinine of ≥ 0.5 mg/dl or a $\geq 25\%$ decrease in eGFR from baseline value at 48 to 72 hours following the exposure of iodine-containing contrast media. Patients were only included if they had a stable kidney function before contrast administration. 124 patients were included. At baseline all patients had a high baseline eGFR (mean eGFR 74 ml/min/1.73m²). Seven patients developed PC-AKI (5.6%). Patients who developed PC-AKI had a mean age of 47 years, mean eGFR 78 ml/min/1.73m², and received a mean volume of iodine-containing contrast of 109 ml. Acute dialysis was not required in any patient. The authors concluded that in kidney transplant recipients with a baseline eGFR >70 ml/min/1.73m², the incidence of PC-AKI is low (Haider, 2015).

Agrawal, 2009 conducted a retrospective study to evaluate the incidence of PC-AKI in kidney transplant recipients. He studied 57 patients for an elective or emergent cardiac catheterization procedure. Two definitions for PC-AKI were used: 1) rise in serum creatinine of 25% or 0.5 mg/dl within 72 hours post-iodine-containing contrast medium exposure, and 2) rise in serum creatinine of 50% or 0.3 mg/dl within 48 days post iodine-containing contrast medium exposure. All patients received peri-procedural hydration with intravenous saline or sodium bicarbonate. The mean age was 58 years. The median baseline eGFR was 52 ml/min/1.73m² (33-90 ml/min/1.73m²). Diabetes was present in 35 patients. The incidence of PC-AKI using the primary definition was 15.5%. This included 1 patient requiring temporary dialysis. The incidence of PC-AKI using the secondary definition was 12.5%. No information was given about the volumes of iodine-containing contrast media used. The authors concluded that PC-AKI is common in kidney transplant recipients (Agrawal, 2009).

Fananapazir, 2016 conducted a retrospective study in kidney transplant recipients. One hundred patients underwent a renal graft arteriography. PC-AKI was defined as an increase in serum creatinine of 0.5 mg/dl or more compared to the creatinine value before arteriography. PC-AKI could be assessed in 37 patients. The mean age was 57

years. Diabetes was present in 48% and hypertension in 100% of patients. All patients received periprocedural hydration with intravenous saline or sodium bicarbonate. Three patients (8%) met the criteria for PC-AKI. At 30 days after the procedure, none of the patients required dialysis or had graft failure. In a subgroup analysis, patients who had an arteriography without angioplasty or stenting, there was a statistically significant higher rate of PC-AKI (Fananapazir, 2016).

4.3 How should a solitary kidney be taken into account when assessing a patient for PC-AKI risk?

Description of studies

There is no evidence that in patients with a solitary kidney the risk of PC-AKI is higher than in patients with bilateral kidneys. No data on intravascular contrast administration are available.

Study results

McDonald (2016) conducted a retrospective study evaluating differences in clinical characteristics and outcomes between the solitary and bilateral kidney groups after intravenous iodine-containing contrast administration. Propensity score matching yielded a cohort of 247 patients with solitary kidneys and 691 patients with bilateral kidneys. Patients were included if they were 18 years or older and underwent contrast-enhanced CT. PC-AKI was defined as an increase in serum creatinine level of either (a) at least 0,5 mg/dl or (b) at least 0.3 mg/dl or 50% over baseline in the 24-72 hours after the CT scan. The mean age of the group of solitary kidney patients was 67 years, of whom 25% had diabetes mellitus. 51% had an eGFR >60 ml/min/1.73m², 49% and eGFR 30-59 ml/min/1.73m², and 0.4 % an eGFR <30 ml/min/1.73m². All patients received intravascular hydration with saline (pre-hydration and post-hydration). The study did not demonstrate any significant differences in the rate of PC-AKI, dialysis, or death attributable to contrast-enhanced CT in patients with a solitary kidney versus bilateral kidneys (McDonald, 2016).

In summary, it is unclear whether patients with a solitary kidney have an increased risk of PC-AKI and whether hydration in these patients will decrease this risk.

4.4 How should the osmolality of iodine-containing contrast medium be taken into account when assessing PC-AKI risk?

Description of studies

A meta-analysis by Eng, 2016 including a total of 17 studies with 4,518 patients who underwent intra-arterial contrast administration, and in whom the risk of PC-AKI was compared between iso-osmolar contrast (IOCM) and low-osmolar contrast medium (LOCM), was included in this analysis. Furthermore, the meta-analysis described a total of 6 studies with 1,405 patients who underwent intra-venous contrast administration, and in whom the risk of PC-AKI was compared between IOCM and LOCM, were also analysed.

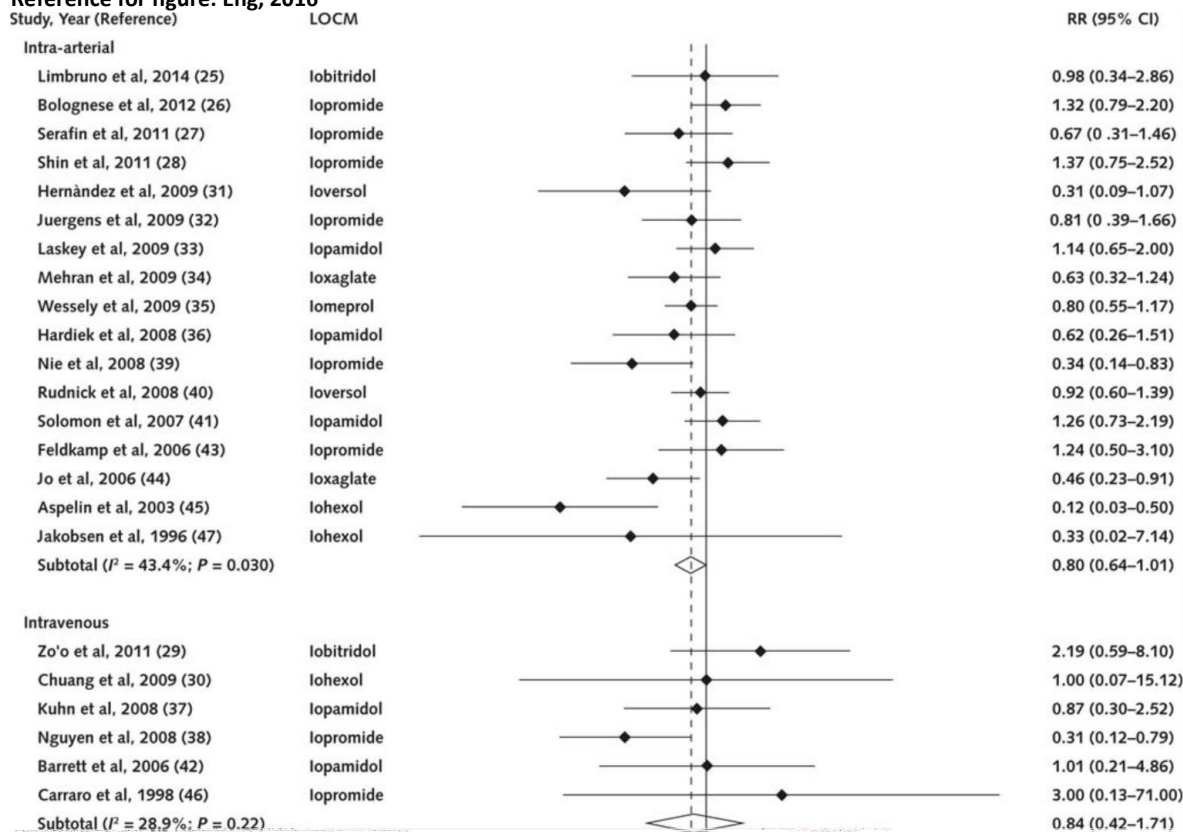
Study results

A pooled analysis of the systematic review by Eng, 2016 is shown below in Figure 4.1. Pooled results of 17 studies in 4,518 patients who underwent intravascular contrast

administration showed a barely significant difference in risk of PC-AKI between iso-osmolar contrast media and low osmolar contrast media (RR: 0.80, 95% CI: 0.64 to 1.01, $p=0.03$), in favour of iso-osmolar contrast media. However, this difference is not clinically relevant if a minimal clinically relevant difference of 10% is applied. Pooled results of 6 studies in 1,405 patients who underwent intra-venous contrast administration find no significant difference in risk of PC-AKI between iso-osmolar contrast media and low osmolar contrast media (RR: 0.84, 95% CI: 0.72 to 1.71, $p=0.22$).

Figure 4.1 Pooled analysis of studies comparing different types of iodine-containing contrast medium.

Reference for figure: Eng, 2016



4.5 Tools for Risk Estimation of PC-AKI

Description of studies

A total of 28 studies with 93,668 patients were identified that developed or validated a model to predict the risk of PC-AKI in patients undergoing either CAG or PCI (intra-arterial contrast administration) (Abellas-Sequeiros, 2016; Araujo, 2016; Aykan, 2013; Bartholomew, 2004; Chen, 2014; Chou, 2016; Duan, 2017; Fu, 2013; Ghani, 2009; Gao, 2014; Gurm, 2013; Inohara, 2015; Ivanes, 2014; Ji, 2015; Kul, 2015; Lazaros, 2016; Lian, 2017; Lin, 2017; Liu, 2016; Maioli, 2010; Marenzi, 2004; Mehran, 2004; Mizuno, 2015; Raposeiras-Roubin, 2013; Sguro, 2010; Tziakas 2013; Tziakas, 2014; Victor, 2014).

Thirteen studies reported on the Mehran Risk score (Abellas-Sequeiros, 2016; Araujo, 2016; Aykan, 2013; Chou, 2016; Gao, 2004; Ivanes, 2014; Jin, 2013; Kul, 2015; Liu, 2016; Maioli, 2010; Mehran, 2004; Mizuno, 2014; Sgura, 2010), this was the most frequently reported risk score. External validation of the Mehran score was performed in 2 studies in 6,852 patients (Maioli, 2010; Mehran, 2004).

No studies were found to design or validate risk stratifications tools for patients undergoing intra-venous contrast administration.

Study results

The summaries of the results of these studies are described in Table 4.10 (Appendix). In most studies only internal validation of the risk model was performed. When external validation of a model was performed, the predictive ability of the model was not strong (AUC <0.8 in most cases). Furthermore, from the information provided in the included studies it was not possible to conclude whether one type of risk model was superior to the other prediction models.

The concordance statistic (c-statistic) or area under a ROC curve (AUC) of the risk model was calculated in numerous studies. These were interpreted as follows:

- A value of 0.5 means that the model is no better than predicting an outcome than random chance;
- Values over 0.7 indicate a good model;
- Values over 0.8 indicate a strong model;
- A value of 1 means that the model perfectly predicts those who will experience a certain outcome and those who will not.

The following risk scores showed a c-statistic or AUC higher than 0.7, indicating that the models were 'good' in predicting PC-AKI: the Mehran score (Abellas-Sequeiros, 2016; Araujo, 2016; Kul, 2015; Lin, 2014; Liu, 2016), the New Preprocedure Risk Score by Duan (2017), the Athens CIN Score (Lazaros, 2016), the risk scores by Chen, Gao, the ACEF, the AGEF, GRACE (Liu, 2016; Gao, 2014)), the risk score by Gurm (2014), the Zwolle risk score (Kul, 2015), the risk score by Lin (2014), the Bartholomew model (Lin, 2014) and the National Cardiovascular Data Register (NCDR) Risk Model of Acute Kidney Injury (Tsai, 2014).

The sensitivity of the tools for risk estimation varied from 42% (CHADS2 score, Chou, 2016) to 94% of the simple risk score of Victor (2014). Based on an external data set Victor (2014) found 92% sensitivity for this risk score. The Mehran score showed up to 79% sensitivity in an acute STEMI patient's population (Aykan, 2014).

Specificity was highest for the Athens CIN Score (Lazaros, 2016), and this was accompanied with a positive predictive value of 77% and a negative predictive value of 87%. Highest reported specificity of the Mehran score was 89% (Aykan, 2013). Specificity of the simple risk score of Victor (2014) was found to be 82% based on an external data set.

The utility of patient questionnaires that can predict impaired kidney function and guide which patients need eGFR evaluation will be discussed briefly in chapter 5 on eGFR evaluation. However, in NL it has been common practice to determine eGFR in all patients receiving intravascular iodine-containing CM and therefore their use is not commonplace.

Quality of evidence

4.1 Risk Factor Analysis for PC-AKI

A summary of risk factors for PC-AKI was made from observational studies with, unfortunately, very low to low quality of evidence.

4.2 to 4.4 Risk Stratification of PC-AKI

Studies comparing contrast administration to no contrast administration

The level of evidence has been graded as low due to the observational nature of the included studies.

For the patients receiving iodine-containing contrast for CT-scan the level of evidence has been graded low, due to downgrading by 2 points: 1 for imprecision and 1 for heterogeneity of included studies.

For the patients receiving iodine-containing contrast for CAG and/or PCI the level of evidence has been graded low, due to downgrading by 2 points for imprecision (wide confidence interval, surpassing borders of clinical relevance).

4.5 Tools for risk evaluation of PC-AKI

Grading of evidence by using the GRADE method was not possible, since this was a diagnostic question. Thus the EBRO methodology was applied (van Everdingen, 2004). The included studies were graded as EBRO B quality.

Conclusions

Risk Factor analysis

	There are no studies that identified risk factors for PC-AKI that can reliably discriminate between risk of AKI and PC-AKI.
Low GRADE	There is a low level of evidence that the risk of PC-AKI was similar in patients who underwent CT-scans with intravenous iodine-containing contrast and those who underwent CT-scans without intravenous contrast. <i>(Bruce, 2009; McDonald, 2013)</i>
Low GRADE	The following risk factors for the development of PC-AKI were consistently identified in multiple studies in patients who underwent a CT-scan and intravenous iodine-containing contrast medium administration: chronic heart failure, diabetes and $eGFR < 60 \text{ mL/min/1.73m}^2$.
Low GRADE	The following risk factors for the development of PC-AKI were consistently identified in multiple studies in patients who underwent CAG and intra-arterial iodine-containing contrast medium administration: chronic kidney disease, multivessel coronary artery disease, older age, heart failure, diabetes, overweight, peripheral vascular disease, metabolic syndrome, and $eGFR < 60 \text{ mL/min/1.73m}^2$, anaemia, albumin, hyperuricemia, proteinuria, use of an intra-aortic balloon pump, contrast volume and emergency PCI.

Very low GRADE	We are uncertain what the risk is of PC-AKI after iodinated CM in patients with a kidney transplant.
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Very low GRADE	We are uncertain what risk is of PC-AKI after iodinated CM in patients with a solitary kidney.
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Type of iodine-containing CM administration

Low GRADE	There is a low level of evidence that iso-osmolar CM administration has a lower risk of PC-AKI than low osmolar CM administration in patients undergoing intra-arterial contrast administration. (Eng, 2016)
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Low GRADE	There is a low level of evidence that iso-osmolar contrast administration has a similar risk of PC-AKI when compared with low osmolar contrast medium administration in patients with undergoing intra-venous contrast administration. (Eng, 2016)
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Tools for estimation of risk for PC-AKI

B EBRO	It is unclear whether one measurement tool for the prediction of PC-AKI risk in patients undergoing intra-arterial contrast administration is superior to another measurement tool to accurately predict this risk in clinical practice. (Aykan, 2013; Bartholomew, 2004; Chen, 2014; Fu, 2012; Ghani, 2009; Gao, 2004; Gurm, 2014; Inohara, 2014; Ivanes, 2014; Jin, 2013; Kul, 2015; Ling, 2015; Maioli, 2012; Marenzi, 2004; Mehran, 2004; Mizuno, 2014; Raposeiras-Roubin, 2014; Sguro, 2010; Tziakas 2013; Tziakas, 2014; Victor, 2014)
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	No studies have been found that study prediction tools for PC-AKI risk in patients undergoing intra-venous iodine-containing contrast administration.
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Considerations

4.1 Risk factors for PC-AKI

Exposure of intravascular iodine-containing contrast media has been associated with the development of PC-AKI. Low- or iso-osmolar contrast medium (LOCM or IOCM) is used for all intravascular CM administration. There is controversy regarding the causal relation between intravascular CM and PC-AKI, since prospective controlled trials are lacking. Moreover, most prospective studies of PC-AKI included patients undergoing coronary angiography or percutaneous coronary intervention. There are several important differences that separate procedures with IA from IV CM administration. First, athero-emboli and hemodynamic instability during cardiac angiography may cause

procedure-related AKI. Second, the cardiac angiography studies thus far lacked a matched control group, and can therefore not discriminate between AKI and PC-AKI. Third, the effect of the concentrated intra-arterial CM bolus given via a catheter may not be generalized to typical IV injections.

In our literature summary we have chosen not to focus on the identification of risk factors that are associated with an increased risk of PC-AKI on top of impaired kidney function, but rather on factors that are associated with a reduction of PC-AKI risk when these patient groups receive hydration. Studies that have described risk factors for PC-AKI have been extracted from the first literature search. Although many factors have been shown to be associated with risk of PC-AKI, it is unclear whether hydration of patients will actually reduce their PC-AKI risk.

4.2 to 4.4 Risk stratification for PC-AKI

The most important methodological limitations regarding observational studies with IV CM is that these studies are not controlled by randomization. For this reason, two large observational studies used PS-matching to compare contrast-enhanced computed tomographic (CT) scan recipients and clinically similar patients who underwent an unenhanced CT scan. Davenport et al showed in a 10-year propensity score-matched retrospective study, including 20,242 hospitalised patients with a stable kidney function, that patients with an eGFR <30 ml/min/1.73m² had a 3-fold increased risk of PC-AKI compared to patients without LOCM enhanced CT (Davenport, 2013b). A limitation of this study is that the risk of PC-AKI was assessed solely in inpatients and that the initial PS-model did not include hydration status. Inpatients are probably older, have a lower eGFR and are at higher risk for AKI than the general population. McDonald, 2015 showed in a 10-year PS-matched retrospective study, including about 12,500 predominantly hospitalised patients with an eGFR ≥ 30 ml/min/1.73m², no evidence of risk of PC-AKI (McDonald, 2014). The risk of AKI following CT examinations, with or without LOCM, was increased in patients with an eGFR <30 ml/min/1.73m². In addition, IV LOCM was not related to excess risk of dialysis or death (McDonald, 2014; McDonald, 2015). In contrast to the study of Davenport, where a single PS model was applied to the entire cohort, the findings of McDonald were derived from propensity scores generated for each distinct CKD group. AKI rates ranged from 1% in the group with eGFR >90 ml/min/1.73m² to 14% in the group with eGFR <30 ml/min/1.73m². A limitation of the studies of McDonald's is that due to the non-randomized design only known confounders were included in their PS-model and unmeasured confounders may have affected the results. In particular, patients who received CM are more likely to have received intravenous hydration or other preventive measures compared with patients who underwent unenhanced CT. In addition, patients who were administered potentially nephrotoxic medications at the time of scanning or who had severe renal impairment may have been less likely to receive CM.

In the Saliña-trial, Kooiman showed in 570 CKD patients that ultra-short hydration with sodium bicarbonate prior to IV CM enhanced CT was non-inferior to peri-procedural saline hydration with respect to risk of PC-AKI. This outcome may result in healthcare savings in The Netherlands (Kooiman, 2014a). Kooiman also studied the risk of PC-AKI in another RCT (Nefros-trial): no hydration vs. sodium bicarbonate hydration (250 ml 1h before CT) in 139 patients with eGFR <60 ml/min/1.73m² undergoing CT-pulmonary angiography. The Nefros-trial showed no difference in risk of PC-AKI and need of dialysis

between both groups. These results suggest that pre-hydration can be safely withheld in CKD patients exposed to IV CM for CT (Kooiman, 2014b).

Apart from preventive hydration, patients should receive adequate volume replacement therapy (with normal saline or Ringer's lactate) if they have clinical signs of hypovolemia, i.e. hypotension, tachycardia, oliguria and / or loss of renal function.

4.5 Risk models or tools for stratification of patient risk

Prediction models which give an accurate estimated risk of developing PC-AKI are of great value and benefit in clinical decision making (Davenport, 2013a). The development of risk prediction models cumulating in prediction models is not a new phenomenon (Davenport, 2013b). The continuing need for these models comes from need of clinicians for easy targeting patients who have a high risk for developing PC-AKI and thus zeroing of preventive measures for those patients not at risk.

A risk prediction model should undergo three analytical phases before putting it in use:

First phase: The risk score or algorithm should be derived from a study that clearly defined its endpoint of interest and that was conducted in a well-defined population.

Second phase: External validation, this should take place in several independent populations.

Third phase: Verification whether the prediction model improves clinical outcome.

The questionnaires that are nowadays in use outside the Netherlands cannot be considered highly valid, since these tools perform poorly when validated externally, and studies verifying whether the application of the prediction model improved clinical outcome are lacking. Web-based tools and apps derived from these questionnaires have the same low level of evidence.

A promising novel tool has been advocated by Gurm (Lenhard, 2013). This web-based and easy to use risk prediction algorithm may prove useful for bedside clinical decision making (Link: <https://bmc2.org/calculators/cin>). A limitation of this tool is that it is primarily focused on patients undergoing PCI procedures, since it was derived from this specific patient population.

Considering all these factors, the Working Group recommends the future development of an easy to use robust tool, which can be used in all cases where iodine-containing contrast is used in patients. Such a tool must be preferably usable in a bedside manner; therefore, a web-based or app solution would be optimal.

Patients with a kidney transplantation and risk of PC-AKI

Given the limited information available in literature, it is unclear whether kidney transplantation patients have an increased risk of PC-AKI and whether hydration of these patients will decrease this risk. Therefore, the Working Group advises to apply the same preventive measures to reduce the risk of PC-AKI in kidney transplantation patient.

Solitary kidney and risk of PC-AKI

According to the Working Group, patients with a solitary kidney do not have an increased risk of PC-AKI and thus recommends that this patient group should be evaluated for PC-AKI in a similar way as patients with bilateral kidneys.

Dialysis patients with residual-diuresis of at least 100 ml/24h

There is no literature available with regard to protection of residual-diuresis in dialysis patients after exposure with iodine-containing CM. Since a residual-diuresis of >100 ml/24h is important for the quality of life, the Working Group recommends to strive for euvolemia before performing any CM-enhanced radiographic investigation in dialysis patients.

Contrast medium dose and risk of PC-AKI

For intravenous iodine-containing CM administration there is no upper dose limit above which the risk of PC-AKI is increased. Nevertheless, the CM dose should be as low as reasonable achievable for a diagnostic study. In modern CT imaging at 70-100 kVp may be used effectively to lower the CM volume (compared to 120 kVp, a reduction of 20-25% at 100 kVp, and 40-50% at 70-80 kVp is feasible).

For intra-arterial iodine-containing CM administration, and especially for interventional procedures, the CM dose with regard to PC-AKI is critical above a certain level. It has been advocated by Nyman et al. to use the *absolute* eGFR that is corrected for body surface area (see also chapter 5) and that the risk of PC-AKI is limited when the administered iodine dose (in gram iodine) to eGFR ratio remains below 1.1 (Nyman, 2008). In the cardiology literature Gurm et al. indicate that the risk of PC-AKI is increased above a CM volume to creatinine clearance (or eGFR) ratio of 3.0. This corresponds at a cut-off level of eGFR 45 ml/min/1.73m² to a CM volume of 135ml.

The Working Group suggests considering the use of these ratios, especially in intra-arterial CM administration with first pass renal exposure. See for explanation Table 4.8 in Appendix below.

According to the Working Group expert opinion hydration is not indicated in hemodynamic stable or euvolemic patients when a low (<30 ml) volume of intra-arterial iodine-containing CM is administered, e.g. for shunt angiography in patients on haemodialysis.

Iodine-containing CM osmolality and risk of PC-AKI

The literature contains conflicting reports about whether IOCM is associated with less risk for AKI than LOCM. The available studies have several limitations. About 7 different LOCM are considered as a group in comparison with one IOCM. Studies generally provided little detail about clinical indications for the diagnostic or therapeutic procedures or other clinical details, such as the severity of the renal impairment, comorbidity, total contrast volume, length of procedure, and contrast injection rates. Studies had to report the incidence of AKI based on serum creatinine levels at baseline and within 72 hours of contrast injection. A more objective picture will be obtained if secondary end points would be evaluated. Relevant secondary end points are the proportion of patients who required specific treatment for acute renal failure, who required dialysis, or who died of acute renal failure at 1 month.

IOCM is isotonic to plasma, but with a much higher viscosity than the LOCM. In animal studies it has been shown that renal iodine-containing CM concentration was increased for IOCM and retention was prolonged 24 hours post injection compared with LOCM injection. Also, enhanced expression of kidney injury markers was found after IOCM injection. These effects were strengthened by severely impaired renal function. Liss et al described in 2006 a higher risk of PC-AKI in patients after IOCM injection in comparison with LOCM injection (Liss, 2006).

The data are further confirmed by a recent propensity score study by McDonald et al. in which 5,758 patients (1538 with stage 1-2 CKD, 2899 with stage 3 CKD, and 1321 with stage 4-5 CKD) were included. After propensity score adjustment, rates of AKI, dialysis, and mortality were not significantly higher in the IOCM group compared with the non-contrast group for all CKD subgroups (AKI odds ratios [ORs], 0.74-0.91, P = .16-0.69; dialysis ORs, 0.74-2.00, P = .42-.76; mortality ORs, 0.98-1.24, P = .39-.88). Sensitivity analyses yielded similar results (McDonald, 2017).

Risks and costs of preventive hydration

From the patients' perspective it is important to notice that hydration with 1L saline pre- and post-iodine-containing CM can harm an individual patient and cause acute heart failure.

Finally, the annual healthcare costs for preventive hydration defined by the CBO 2007 guideline are estimated to be 60 million euros. These costs are substantial, especially when considering that the clinical relevance of PC-AKI is still under debate.

In summary, IV administered iodine-containing CM is most likely a weak independent nephrotoxic risk factor in patients with stable eGFR of less than 30 ml/min/1.73m², for which hydration might be needed to prevent PC-AKI. IV CM does not appear to be a risk factor in patients with stable eGFR between 30 and 60 ml/min/1.73m².

When iodine-containing CM is administered intra-arterially, it is most likely an independent risk factor for PC-AKI in patients with stable eGFR of less than 30 ml/min/1.73m², therefore hydration is needed to prevent PC-AKI.

Appendix: A little help for interpretation of contrast enhanced CT studies

The most relevant CM injection parameter for enhancement in CT of solid organs (e.g. liver) is usually the CM Dose (in mgl) which is equivalent to CM volume x CM concentration. Typical values range from 30,000-60,000 mgl, depending on body weight for CT at 120 kVp.

The most relevant parameter for enhancement in CT angiography or for arterial enhancement in CT of organs (e.g. liver, pancreas, adrenal glands) is the CM Iodine Delivery Rate or Iodine Flux (in mg Iodine/s), which is equivalent to CM injection rate x CM concentration. For large vessels typical values range from 1200-1500 mgI/s and for smaller vessels 1600-2000 mgI/s for CT at 120 kVp.

As noted above, because of increased signal of iodine-containing CM at lower tube voltages, a voltage of 70-100 kVp may be used effectively to lower the iodine-containing CM dose. In comparison to 120 kVp a reduction in CM volume of 20-25% at 100 kVp and

40-50% at 70-80 kVp is feasible. For the same reason low kVp imaging is also an effective way to reduce iodine loads in patients with renal impairment (Nyman, 2011).

A range of iodine-containing CM concentrations of various agents are in clinical use and Table 4.8 provides a help for conversion of iodine dose (in mg Iodine) to CM volume (in ml) and vice versa.

Table 4.8 Conversion of CM dose (in mgl) to CM volume (in ml) for CM concentrations @ 120 kVp

CM Dose in mgl	CM concentration in mgl/ml					
	270	300	320	350	370	400
5,000	19	17	16	15	14	13
10,000	37	33	31	29	27	25
20,000	74	67	63	58	54	50
30,000	111	100	94	86	81	75
45,000	166	150	141	128	122	113
60,000	222	200	188	171	162	150

Recommendation

Optimal nephrology care should be the primary goal in all chronic kidney disease patients, especially with attention to hydration status and medication use.

Consider an alternative imaging technique that does not require iodine-containing CM in all patients with an increased risk of PC-AKI.

Consult a nephrologist/internist for patients with an eGFR <30 ml/min/1.73m².

Aim for clinical euolemia, using normal saline or Ringer's lactate, before administration of intravascular iodine-containing CM, regardless of eGFR.

For patients undergoing intravascular administration of iodine-containing CM:
Consider patients with an eGFR <30 ml/min/1.73m² at risk for PC-AKI.

Apply the same recommendations, indicated for patients with bilateral kidneys, to patients with a solitary kidney or kidney transplantation subjected to iodine-containing contrast administration.

Consider that low osmolar contrast media and iso-osmolar contrast media have the same renal safety profile.

Do not use prediction models or tools to estimate the risk of PC-AKI, since their validity and effect on clinical outcome is unclear.

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Chapter 5 Evaluation of estimated glomerular filtration rate (eGFR)

Clinical question

How to assess kidney function before and after iodine-containing contrast administration?

Sub questions

- 5.1 What is the best way to assess renal function?
- 5.2 When should an eGFR calculation be performed prior to contrast administration?
- 5.3 When should an eGFR calculation be performed after contrast administration?
- 5.4 If PC-AKI is diagnosed, how should the patient be followed-up?
- 5.5 How long are eGFR calculations valid?

Introduction

Currently, the measurement of creatinine using Isotope Dilution Mass Spectrometry (IDMS) is standardized. Worldwide standardization of creatinine measurement has been accomplished, but selectivity issues remain due to persistence of non-selective methods leading to inaccurate creatinine and eGFR results. It is the end-responsibility of the lab professional to select and implement accurate - selective - creatinine measurement methods for adequate patient care.

In addition, it should be noted that glomerular filtration rate (GFR), defined as ml/minute passing through the kidneys as a substitute for kidney function, essentially differs from creatinine clearance which is defined as: $\text{Urinary volume} * ([\text{creatinine}]_{\text{urine}} / [\text{creatinine}]_{\text{plasma}})$. In case of creatinine clearance, especially with low kidney filtration, creatinine clearance may exceed GFR up to 25% due to active tubular secretion of creatinine.

Assessment of eGFR in children is outside the scope of this guideline. Specific equations for the calculation of eGFR for children and elderly may be found elsewhere (Pottel, 2016; Schwartz, 2009; Schöffner, 2012). In addition, it is not necessary to adapt the CKD-EPI formula for patients >70 years of age.

Serum or plasma creatinine is the medical test of choice for evaluating kidney function in every laboratory in the Netherlands. Due to extensive standardization efforts both at the international and the national level, the inter-laboratory variability is far below 10%. As a result of ongoing improvements in creatinine assays, methods are now available for selective measurement of creatinine with high reproducibility and small variation. As a consequence of the low analytical (total CVa <2%) and biological variability (CVw = 4-7%), creatinine measurement is currently the most suitable test for assessment of kidney function. On the basis of its high reproducibility and low variability, the serum or plasma creatinine test is suitable for detection of minimal changes during treatment (Fraser, 2011), for monitoring kidney function after kidney transplantation or after contrast medium application, and for monitoring of disease progression.

Currently no alternative test of kidney function other than creatinine is available that is reimbursed and offers high analytical reliability and low biological variation. The use of beta-trace and Cystatin C has not been validated adequately for large cohorts and these tests are not widely available in Dutch clinical chemistry laboratories.

The current use of generic and broad reference values for creatinine covers up significant changes of kidney function within the reference interval. In addition, the use of broad reference values does not permit the follow-up of vulnerable patients with slowly deteriorating kidney function. As a consequence, it is suggested that in vulnerable patients, measurement of creatinine with increased frequency leads to early detection of kidney function deterioration. Using the formula for determination of the critical difference based upon individual and analytical variability (Fraser 2011), a deterioration of kidney function can be detected with high reliability. Applying a analytical and biological variation of 2% and 5% respectively (see above), a critical difference is detected with 95% certainty (Z value 1,96, Critical difference (%) = $1,96 * \sqrt{2} * \sqrt{v(CVa) + v(CVw)}$) when the two consecutive measurements of creatinine differ by at least 14,9%, e.g. when a value of 100 $\mu\text{mol/L}$ increases to at least 115 $\mu\text{mol/L}$ or a value of 150 $\mu\text{mol/L}$ increases to at least 173 $\mu\text{mol/L}$.

Following the recent validation of the CKD-EPI formula in a large cohort by Levey et al. (Levey, 2009) and by using serum creatinine standardized to the IDMS reference system, the use of the CKD-EPI equation in Dutch hospitals has been deemed feasible. The use of additional formulas, e.g. the Lund-Malmö Revised equation is not deemed usable given the specific Swedish (Caucasian) population from which this formula was derived and validated (Nyman, 2014). As per 2015, the Dutch SKML chemistry section advises the use of the creatinine based CKD-EPI formula given its improved performance for CKD risk classification compared to the MDRD formula around the clinical decision limit of 60 ml/min/1.73m².

In case the patient's specific body surface area (BSA) is available, eGFR can be adjusted for BSA (also termed absolute eGFR) (Nyman, 2014).

Based upon a recent pilot study on differences in type and severity of comorbidity (Björk, 2010) and by using techniques of population weighted means, it can be estimated whether a patient has an eGFR <60 ml/min/1,73m² or ≥60 ml/min/1,73m². By stratifying patients according to their algorithms, the authors came to a preselection of patients with low or normal kidney function. In case a preselection is available of patients with increased risk for CKD or CIN follow up of these patients may be adjusted. The efficacy of these stratification studies however needs evaluation for the Dutch setting.

What is the best way to assess renal function?

Assessment of kidney function is preferable from a single measurement of an endogenous filtration marker. So far, several biomarkers have been evaluated (e.g. creatinine, Cystatin C, beta trace), although only creatinine has thus far found widespread use in most clinical chemistry laboratories. Serum creatinine measurements are the basis for creatinine-derived eGFR estimates. Historically, routine measurement of creatinine was performed using colorimetric Jaffe methods. The Jaffe method is however a chemical method affected by non-specificity since not only creatinine reacts

with the alkaline picrate but also other analytes such as serum protein and glucose (Cobbaert, 2009).

The quality of the eGFR estimates is strongly dependent on serum creatinine measurement accuracy. For this reason, selective measurement of serum creatinine with analytical performance in line with desirable bias and imprecision criteria based on biological variation is paramount for guaranteeing metrological traceability. It should be kept in mind therefore that adequate risk classification using GFR critically depends on universal standardization and application of selective creatinine measurement procedures.

Following the first large study published in 1999 to estimate glomerular filtration rate (eGFR), from creatinine (Levey, 1999), the MDRD formula was further improved by using isotope dilution mass spectrometry (IDMS), (Levey, 2006) and is now subsequently replaced by the CKD-EPI equation (Levey, 2009; van den Brand, 2011). This succession of eGFR formula therefore illustrates an ongoing effort of methods to accurately estimate GFR rather than a defined endpoint. In brief, the advantage of the CKD-EPI equation is the higher accuracy of eGFR predictions for normal kidney function than the MDRD equation. In addition, following the introduction of the CKD-EPI equation, a reduced number of patients is misclassified as compared with the MDRD equation, especially for eGFR values <60 ml/min/1.73m².

Kidney function is likely stable in patients without chronic kidney disease. Extensive risk prediction model development has indicated that underlying comorbidities such as chronic kidney disease, increased age, heart failure or impaired ejection fraction, hypotension, hypertension or shock may correlate with the possible development of AKI but are not specific for PC-AKI. The applicability of current risk models in clinical practice is only modest (Silver, 2015).

With the use of an endogenous filtration marker it should be noted that any endogenous marker is influenced by several non-GFR determinants, such as body mass, diet, racial background, gender etc. Important considerations are that eGFR is unreliable in patients with acute kidney failure and may overestimate renal function in patients with a reduced muscle mass. When adapted for specific subpopulations e.g. on the basis of descent, improvements may be possible for eGFR values, this however lies outside of the scope of this guideline.

When should an eGFR calculation be performed prior to contrast administration?

Kidney function, assessed by eGFR is, according to the working group, likely stable in patients without chronic kidney disease or, underlying comorbidities such as heart failure or, hypertension and in the absence of the use of nephrotoxic medication. In these patients, considered to have normal kidney function, an eGFR measurement should be available within approximately 12 months before any CT imaging or angiography with or without intervention with the possible use of a contrast agent. Patients who are followed-up for oncological diseases are also included in this category.

It is the opinion of the working group that an eGFR result should not be more than 3 months old in patients with CKD, a known other chronic disease or the use of nephrotoxic drugs. Chronic disease is defined in analogy to WHO criteria: chronic or non-

communicable diseases are of long (more than 3 months) duration and generally slow progression. The main types are cardiovascular diseases, diabetes, chronic kidney diseases, chronic respiratory system diseases, chronic gastro-intestinal diseases, and chronic connective tissue and auto-immune diseases. (http://www.who.int/topics/noncommunicable_diseases/en/).

In patients with any acute disease or an acute deterioration of a chronic illness a recent eGFR, not more than 7 days old, is needed before CM administration. Frequently occurring examples include acute infections, acute cardiovascular diseases, acute gastro-intestinal diseases, respiratory diseases, acute kidney diseases, and acute connective tissue and auto-immune diseases. Also for all patients admitted to a hospital an eGFR <7 days old is needed before CM administration.

The nephrotoxicity of gadolinium-based contrast agents and/or microbubble contrast media and the recommendations for measurement of eGFR will be integrated with the guidelines for prevention of Nephrogenic Systemic Fibrosis. These will be published in the guideline Safe Use of Contrast Media, part 2 (due beginning of 2019).

When should an eGFR calculation be performed after the contrast administration?

There is no clear consensus guidance in the literature on this point. According to the Working Group, eGFR should be determined within 2-7 days after contrast administration in every patient with high risk for developing PC-AKI that receives preventive hydration. In patients requiring the continuation of metformin, an eGFR should be measured within 2 days. In most patients, a decreased kidney function may spontaneously resolve.

In patients without chronic kidney disease or, underlying co-morbidities such as heart failure, hypertension and not using nephrotoxic medication prior to the CM administration an eGFR determination after CM administration can be omitted.

If PC-AKI is diagnosed, how should the patient be followed-up?

In studies, eGFR was assessed after 2-3 days after CM administration to diagnose PC-AKI. In case PC-AKI is diagnosed within 2-7 days, additional follow-up is mandatory. It is the expert opinion of the Working Group that further follow-up is mandatory for patients in whom PC-AKI is diagnosed, for at least 30 days post-diagnosis with re-assessment of PC-AKI.

Emergency patients / procedures

In case of a major life-threatening medical condition requiring rapid decision-making including emergency imaging or intervention (e.g. stroke), the determination of the eGFR can be postponed or the imaging or intervention can be started while the eGFR is being determined in the laboratory. If the possibility exists to wait a short time before commencing diagnosis or intervention, without doing harm to the patient, eGFR should be determined immediately, and if indicated, individualized preventive measures should be taken before the administration of intravascular iodine-containing contrast medium.

Patient Questionnaires

In the Netherlands, for practical purposes the VMS Quality Project (VMS, 2009) has introduced to measure eGFR before every iodine-containing CM administration which has gained wide acceptance. This is not in accordance with scientific data which suggest that eGFR measurements can be performed only in patients at risk. Based on previously published risk factors (see also chapter 13 on Risk Stratification) several patient questionnaires to guide clinicians when to assess eGFR have gained popularity, especially the 6-question questionnaire (Choyke, 1998); which formed the basis for the more extensive questionnaire for multiple aspects of CM safety by the ESUR Contrast Media Safety Committee (Morcos, 2008).

For PC-AKI prevention when a contrast-enhanced examination with iodine-containing CM is planned, these questionnaires ask the patient and referring physician about: history of renal disease, history of renal surgery, and the presence of heart failure, diabetes, proteinuria, hypertension or gout. It has been shown that these simple questionnaires are sensitive in identifying patients with eGFR <45 ml/min/1.73m² and can reduce the need for eGFR assessments via laboratory or point-of-care techniques, especially in patients younger than 70 years (Azzouz, 2014; Too, 2015; Zähringer, 2015).

Searching and selecting literature

No literature search was performed for this chapter, since the clinical questions presented in this chapter could not be answered by literature but by consensus of the working group.

Summary of literature

No literature search was performed for this chapter, since the clinical questions presented in this chapter could not be answered by literature but by consensus of the working group.

Conclusions

No literature search was performed for this chapter, since the clinical questions presented in this chapter could not be answered by literature but by consensus of the working group.

Formulas

MDRD equation (Levey, 2006)

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{Cr} / 88.4)^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)} \\ \times 1.210 \text{ (if African American)}$$

CKD-EPI equation (Levey, 2009)

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = \begin{array}{ll} \text{Female Cr} \leq 62 \mu\text{mol/l: } & 144 \times (\text{Cr} / 62)^{-0.329} \times 0.993^{\text{Age}} \\ \text{Female Cr} > 62 \mu\text{mol/l: } & 144 \times (\text{Cr} / 62)^{-1.209} \times 0.993^{\text{Age}} \\ \text{Male Cr} \leq 80 \mu\text{mol/l: } & 141 \times (\text{Cr} / 80)^{-0.411} \times 0.993^{\text{Age}} \\ \text{Male Cr} > 80 \mu\text{mol/l: } & 141 \times (\text{Cr} / 80)^{-1.209} \times 0.993^{\text{Age}} \end{array}$$

x 1.159 (if African American).

Note that Cr denotes creatinine concentration in both plasma and serum in $\mu\text{mol/L}$.

Selected eGFR calculator links:

National Kidney Foundation (US)

https://www.kidney.org/professionals/kdoqi/gfr_calculator

National Institute of Diabetes and Digestive and Kidney Diseases (US)

<http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/Pages/gfr-calculators.aspx>

Recommendations

Physicians/ clinicians

Determine eGFR in each patient scheduled for Computed Tomography or Angiography with or without intervention with use of intravascular iodine-containing contrast media prior to CM administration.

The measurement of eGFR is valid for:

- maximally 7 days when the patient has an acute disease or an acute deterioration of a chronic disease;
- maximally 3 months when the patient has a known chronic disease with stable renal function;
- approx. 12 months in all other patients

Determine eGFR within 2 to 7 days after intravascular contrast administration in every patient for whom preventive measures against PC-AKI were taken.

If PC-AKI is diagnosed (by KDIGO criteria), follow the patient for at least 30 days post-diagnosis and re-assess serum creatinine.

Laboratory specialists

Measure the serum or plasma creatinine using a selective (enzymatic) method.

Implement the creatinine based CKD-EPI formula for estimation of the eGFR.

Consider correcting the eGFR for BSA in the CKD-EPI formula in case that the patient's specific body surface area (BSA) is known.

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Chapter 6 Prevention: Hydration and Complications

Clinical question

What hydration strategy should be recommended for patients undergoing radiologic or cardiologic examinations with intravascular iodine-containing contrast media?

Several sub questions arise when it comes to this particular subject:

- 6.1. Is there a significant difference in the incidence of PC-AKI comparing hydration versus no hydration?
- 6.2. Is there a significant difference in the incidence of PC-AKI comparing oral versus intra-venous pre- and post-hydration?
- 6.3. Is there a significant difference in the incidence of PC-AKI comparing intra-venous NaCl versus NaHCO₃?
- 6.4. Is there a significant difference in the incidence of PC-AKI comparing intravenous pre-hydration versus pre- and post-hydration?
- 6.5. Is there a significant difference in the incidence of PC-AKI in patients undergoing controlled diuresis versus standard hydration schedules?

Introduction

When it comes to prevention of PC-AKI, the cornerstone is hydration (volume expansion). In the literature, many hydration schedules, hydration fluids and routes of administration have been described. These schedules have been rubricated into the 5 above mentioned categories.

Literature search and selection

To answer our clinical question a systematic literature analysis was performed for the following research question:

What type of hydration reduces the risk of contrast-associated acute kidney injury best in patients undergoing radiological examinations with intravascular contrast administration?

P (patient category)	patients undergoing radiological examinations with iodine-containing contrast media;
I (intervention)	hydration with NaCl i.v., hydration with bicarbonate, oral hydration, hydration, pre- and posthydration;
C (comparison)	one of the forms of hydration described above or no hydration;
O (outcome)	post-contrast acute kidney injury (PC-AKI), start dialysis, decrease in residual kidney function, cost-effectivity.

Relevant outcome measures

The working group considered PC-AKI, mortality, start dialysis, decrease in residual kidney function, critical outcome measures for the decision making process and adverse effects of hydration and cost-effectivity important outcome measures for the decision-making process. The working group defined the outcome measure PC-AKI as described in the introduction of the Guideline.

A difference of at least 10% in relative risk was defined as a clinically relevant difference; by expert opinion of the working group (no literature was available to substantiate the decision). To illustrate, if PC-AKI occurs with an incidence of 10% in the patient population, a difference of 10% of relative risk would mean a difference of 1% in absolute risk. Thus, the number needed to treat would be 100, ergo: a doctor would need to treat 100 patients to prevent one case of PC-AKI. When the incidence of PC-AKI is 5%, a difference of 10% in relative risk would mean a difference of 0.5% in absolute risk, and a number needed to treat of 200.

Search and select (method)

The databases Medline (OVID), Embase and the Cochrane Library were searched from January 2000 to 17th of June 2015 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). Search terms are shown in the Appendix. The literature search procured 858 hits: 183 SRs, 572 RCTs and 103 OBS. An update of the search on April 14th 2017 retrieved an additional 138 studies.

Studies were selected based on the following criteria:

- Adult patients who underwent radiological examination using contrast media (including radiological examination during percutaneous angiography);
- Patients with impaired kidney function, at least eGFR <60 ml/min/1.73m²;
- Hydration types: hydration with NaCl i.v., hydration with bicarbonate, oral hydration, pre-hydration, pre- and posthydration;
- At least one of the outcome measures was described: Post-contrast acute kidney injury (PC-AKI), Contrast-induced nephropathy (CIN)/contrast-induced acute kidney injury (CI-AKI), start dialysis, decrease in residual kidney function, adverse effects of hydration (overfilling, intensive care unit admittance, mortality), cost-effectivity;
- Follow-up time after hydration was at least 48 hours.

Based on title and abstract a total of 47 studies were initially selected, and a total of 17 studies based on the updated search (64 in total). After examination of full text a total of 19 + 10 (29 in total) studies were excluded and 28 + 7 studies definitely included in the literature summary.

Results

Thirty-five studies were included in the literature analysis, the most important study characteristics and results were included in the evidence tables. The evidence tables and assessment of individual study quality are included.

Summary of literature

1. Hydration versus no hydration:

Description of studies

Six RCTs were found for this comparison (Chen, 2008; Jurado-Roman, 2015; Kooiman 2014; Luo, 2014; Maioli, 2011; Nijssen, 2017).

Three of these involved comparisons for patients undergoing primary percutaneous intervention (PCI). Both Jurado-Roman, 2015, Luo, 2014 and Maioli, 2011 included

myocardial infarction patients needing immediate PCI. In all 3 studies, the majority of patients had eGFR >60 ml/min/1.73m², therefore these studies were excluded in the analysis.

Chen, 2008 used half saline (NaCl 0.45%) as hydration fluid and only the patients with impaired kidney function received NAC orally. For these two reasons, this study was excluded from the analysis. Thus only two studies were included in the literature analysis.

Kooiman, 2014 described 138 patients with eGFR <60 ml/min/1.73m² undergoing chest CT for suspected pulmonary embolism. Sixty-seven patients received no hydration and the remaining 71 patients received 250ml NaHCO₃ 1.4% within one hour prior to CT.

Nijssen, 2017 included 660 high risk patients (≥18y), as indicated by the local (Dutch) and European guidelines, with an eGFR of 30-59 mL per min/1.73m² undergoing an elective procedure requiring ionidated contrast material which were randomly assigned to: (1) intravenous NaCl (0.9% NaCl 3-4 ml/kg/h during 4 hrs pre- and postcontrast) (n=332) or (2) no prophylaxis (n=328). Of Note: 48% of patients received the long hydration protocol, 12 hours pre- and 12 hours post-contrast.

Results

Kooiman, 2014 reported a PC-AKI incidence of 8.1% in the group withholding hydration versus 7.1% in the group with 1-hour pre-hydration with 250ml NaHCO₃, RR: 1.29 (95%CI: 0.41 to 4.03). None of the PC-AKI patients developed need for dialysis.

Nijssen, 2017 reported that PC-AKI occurred in eight (2.7%) of 296 intravenously hydrated patients and in eight (2.6%) of the no-prophylaxis patients, with a nonsignificant absolute difference in proportions of -0.1% (one-sided 95% CI: -2.25 – 2.06, one-tailed p=0.471).

Quality of evidence

The level of evidence was graded as low for Kooiman, 2014 due to imprecision and indirectness (only patients with suspicion of pulmonary embolism were included); thus the evidence was downgraded by 2 levels. The level of evidence was graded as moderate for Nijssen, 2017, downgraded 1 level, due to imprecision. Power analysis indicated that 1300 patients would give a reasonable (80%) chance of detecting a difference between groups (as estimated using the expected H+ group CIN incidence 2.4%, a non-inferiority margin 2.1%, and given a conventional level of alpha (0.05), only 660 patients were included. (Nijssen, 2017)

2. *Oral versus intravenous hydration:*

Description of studies

A total of nine RCTs on this subject have been published, but only two were considered suitable to be included in this literature summary. Four RCTs included patients with normal kidney function (Trivedi, 2003; Kong, 2012; Akyuz, 2014; Martin-Moreno, 2015). Two RCTs described a mixture of oral and intravenous hydration, compared to intravenous hydration alone (Taylor, 1998; Lawlor 2007). One RCT did not define PC-AKI (Wrobel, 2010), only describing serum creatinine changes. The last excluded RCT described 4 research arms, three with intravenous hydration and one with extra NaCl

orally, but no extra fluid orally. Therefore, this RCT was excluded (Dussol, 2006). One RCT (Cho, 2010) was considered suitable for inclusion in the literature summary.

Cho, 2010 the RCT using both pre- and post hydration consisted of 91 patients with sCr >97,2µmol/l or GFR <60 ml/min/1.73m² undergoing elective CAG. They were randomly assigned into 4 groups: A, NaCl 154mEq (0.9%)/l 3ml/kg/h 1 hour pre and 1ml/kg/h 6 hours post CM. B. NaHCO₃ 154mEq/l, same schedule as NaCl. C. 500ml of water, 4-2 hours pre CM administration, followed by 600ml of water post contrast administration. D, C + 3.9g oral NaHCO₃ pre CM and 1.95g oral NaHCO₃ post CM.

Results

Cho, 2010 also found no significant difference in the incidence of PC-AKI in all 4 groups; A 22.2%, B 9.5%, C 4.5% and D 4.8% (p>0.05).

Quality of evidence

For the comparison oral versus intravenous hydration in all patients the level of evidence was graded as low due to imprecision and heterogeneity of included studies.

3. *Saline (sodium chloride) versus sodium bicarbonate hydration:*

Description of studies

Depending on the design, the RCTs comparing sodium to bicarbonate hydration were categorized into several groups:

1. Short schedule NaHCO₃ vs. short schedule NaCl in patients with impaired kidney function undergoing coronary angiography (CAG) and/or PCI. A total of 10 RCTs (Adolph, 2008; Boucek, 2013; Brar, 2008; Gomes, 2012; Manari, 2014; Masuda, 2007; Ozcan, 2007; Ratcliffe, 2009; Recio-Mayoral, 2007; Solomon 2015) with 2,408 patients were identified, that compared bicarbonate and saline hydration in a similar hydration scheme for coronary angiography. All the studies were performed in patients with impaired kidney function;
2. Short schedule NaHCO₃ vs. long schedule NaCl (1ml/kg/h for 12h pre- and 12h post-CM administration) in patients with impaired kidney function undergoing CAG and/or PCI. A total of 9 RCTs (Briguori, 2007; Castini, 2010; Hafiz, 2012; Klima, 2012; Koc 2013 Lee, 2011; Maioli, 2008; Nieto Rios, 2014; Shavit, 2009) with 3,026 patients were identified that compared bicarbonate hydration to saline pre- and posthydration (1ml/kg, 12hour pre- and post) for coronary angiography;
3. All other hydration schedules comparing bicarbonate plus saline to saline or to bicarbonate only. Four RCTs (Chong, 2015; Motohiro, 2011; Tamuro, 2009; Ueda, 2011) with 358 patients compared bicarbonate to saline hydration with divergent hydration schemes for coronary angiography, like adding a bolus NaHCO₃ to saline hydration or exchanging saline by NaHCO₃ hydration for multiple hours;
4. One RCT compared in a non-inferiority trial, a 1-hour schedule of 250ml NaHCO₃ 1.4% versus 1000 ml NaCl 0,9% in 4-12h pre- and 4-12h post-CM administration in 548 CT patients. (Kooiman, 2014).

Results

Depending on the design, the RCTs comparing sodium to bicarbonate hydration were categorized into several groups:

1. Short schedule NaHCO₃ (3ml/kg/h 1 hour pre and 1ml/kg/h 6 hours post CM administration) vs. short schedule NaCl in patients with impaired kidney function

undergoing CAG and/or PCI. A total of 10 RCTs with 2,408 patients and 288 PC-AKI events were indentified (Adolph, 2008; Boucek, 2013; Brar, 2008; Gomes, 2012; Manari, 2014; Masuda, 2007; Ozcan, 2007; Ratcliffe, 2009; Recio-Mayoral, 2007; Solomon 2015). No significant difference was found between patients that underwent bicarbonate versus saline hydration: Risk Ratio (RR): 0.88 (95% CI: 0.51 – 1.50), $p=0.63$, $I^2=60\%$, as shown in Figure 6.1;

2. Short schedule NaHCO_3 (3ml/kg/h 1 hour pre and 1ml/kg/h 6 hours post CM administration) vs. long schedule NaCl (1ml/kg/h 12 hours before and after CM administration) in patients with impaired kidney function undergoing CAG and/or PCI. A total of 9 RCTs (Briguori, 2007; Castini, 2010; Hafiz, 2012; Klima, 2012; Koc 2013; Lee, 2011; Maioli, 2008; Nieto Rios, 2014; Shavit, 2009) with 2,994 patients and 272 PC-AKI events were identified that compared bicarbonate hydration to saline pre- and posthydration (1ml/kg, 12hour pre- and post) for coronary angiography. No significant difference was found between patients that underwent bicarbonate versus saline hydration: Risk Ratio (RR): 1.23 (95% CI: 0.81 – 1.87), $p=0.33$, $I^2=47\%$ as shown in Figure 6.2;
3. All other hydration schedules comparing bicarbonate plus saline to saline or to bicarbonate only. A total of 4 RCTs (Chong, 2015; Motohiro, 2011; Tamura, 2009; Ueda, 2011) with 668 patients and 58 PC-AKI cases, were considered suitable for this literature summary. The studies were considered too heterogenous in terms of hydration fluid content and hydration schemes in control group and treatment group to be considered for pooling. Chong, 2015 reported that PC-AKI incidences were 10/153 (6.5%) in the group receiving NaCl plus NAC, and 16/151 (10.6%) in the group bicarbonate plus NAC. The difference in PC-AKI incidence between groups was not significant. Motohiro, 2011 reported that 2/78 patients in the bicarbonate plus saline group versus 10/77 in the standard hydration group (RR: 0.20, 95% CI: 0.04 to 0.87) developed PC-AKI, thus the incidence of PC-AKI was lower in the combination group. Tamura, 2009 also reported lower rates of PC-AKI in the bolus group: 1/72 versus 9/72 (RR: 0,11; 95% CI: 0.01 to 0.85. The results of Ueda, 2011 were similar, although the difference in incidence of PC-AKI was not statistically significant: 2/30 versus 8/29 PC-AKI cases; RR: 0.24 (95% CI: 0.06 to 1.04);
4. Kooiman, 2014 reported a PC-AKI incidence of 4.1% in CT patients receiving 250ml NaHCO_3 (ultrashort schedule) precontrast versus 5.1% ($p=0.23$) receiving pre- and post-CM hydration with NaCl 0,9%. No patients developed a need for dialysis.

The risk of mortality, dialysis requirement and cardiovascular complications of hydration (such as pulmonary edema) are shown in Table 6.1 for all the saline versus sodium bicarbonate hydration comparisons. The number of adverse events was often not reported, and when reported was low. In the Kooiman 2014 study, mentioned in the paragraph above, Acute heart failure due to volume expansion (based on the treating physician's clinical judgement) occurred in none of the patients in the NaHCO_3 group versus 6 of 281 patients in the saline group ($p = 0.03$). Consequently, NaCl 0,9% hydration was prematurely stopped in 1 of 281 patients. (Kooiman, 2014).

Quality of evidence

For the comparison bicarbonate versus saline, the level of evidence was graded as low (downgraded by 2 levels) due to heterogeneity and imprecision. For the comparison bicarbonate bolus versus saline bolus hydration for emergency angiography, followed by

bicarbonate hydration in both groups, the level of evidence was downgraded with one more level for imprecision (very low number of events).

4. *Pre-hydration only versus pre- and posthydration:*

Description of studies

One RCT compared in a non-inferiority trial, a 1-hour schedule of 250ml NaHCO₃ 1.4% versus 1000 ml NaCl 0,9% in 4-12h pre- and 4-12h post-CM administration in 548 CT-patients. (Kooiman, 2014).

Results

Kooiman, 2014 reported a PC-AKI incidence of 4.1% in CT patients receiving 250ml NaHCO₃ (ultrashort schedule) pre-contrast versus 5.1% (p=0.23) receiving pre- and post-CM hydration with NaCl 0,9%. No patients developed a need for dialysis.

Quality of evidence

This non-inferiority study from the Netherlands has sufficient number of patients, therefore the evidence was graded as moderate.

5. *Hydration with controlled diuresis:*

Description of studies

Five Italian studies, all RCTs, describe the same technique, consisting of an extracorporeal circuit for continuous fluid infusion, combined with a Foley catheter for measuring urinary production (Barbanti, 2015; Briguori, 2011; Marenzi, 2012; Usmiani, 2016; Visconti, 2016) in respectively 112, 292, 170, 123, and 48 patients. This system is capable of delivering sterile replacement solution in an amount matched to the volume of urine produced, thereby avoiding hypovolemia and fluid overload. It displays urine and replacement volume and alerts to replace the fluid bag or drain the urine bag. After an initial bolus of 250ml NaCl 0.9% infused over 30 minutes, patients receive furosemide, 0.25mg/kg, to achieve a urinary flow of at least 300ml/h. Once this is achieved, the procedure is performed. The system keeps urinary flow >300ml/h for the next 4 hours, balancing between more NaCl and low dose furosemide.

Two of these three papers describe patients undergoing CAG and/or PCI (Marenzi, 2012; Usmiani, 2016), two papers describe patients undergoing Transcatheter Aortic Valve Implantation (TAVI) (Barbanti, 2015; Visconti, 2016) and one describes a mixed group of CAG and peripheral angiography (Briguori, 2011). All patients had eGFR <60 ml/min/1.73m², in one paper <30 ml/min/1.73m² (Briguori, 2011). The control group of each study had a different hydration schedule (saline versus bicarbonate versus a combination of both). Therefore, pooling of the studies was not possible due to heterogeneity.

Regarding the control group, Briguori, 2011 used 154 mEq/L of sodium bicarbonate in dextrose and water, mixed in the hospital pharmacy by adding 154mL of 1000 mEq/L sodium bicarbonate (i.e. sodium bicarbonate 8.4%) to 846 mL of 5% dextrose in water (D5W), slightly diluting the dextrose concentration to 4.23%. 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. All patients enrolled in this group received 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). In this group, an additional NAC dose (1200 mg diluted in 100 mL normal saline) was administered intravenously during the procedure. The total NAC dose was 6g.

The control group of Marenzi, 2012 received a continuous intravenous infusion of isotonic saline at a rate of 1 ml/kg/h (0.5 ml/kg/h in case of left ventricular ejection fraction <40%) for at least 12 h before and 12 h after the procedure. The control group of Usmiani, 2016 received 1000 mL isotonic saline i.v. administration 12 h before procedure (rate-adjusted according to LVEF: 20–40 mL/h if LVEF <30%, 80–120 mL/h if LVEF 30–50%, 200 mL/h if LVEF >50%), plus 3 mL/kg/h sodium bicarbonate 1.4% solution by i.v. infusion for 1 h before procedure, plus 5000mg of Vitamin C and 1200mg NAC administered orally. After the procedure the patients received 1 mL/kg/h sodium bicarbonate 1.4% solution iv for 6 hours, plus 5000mg of vitamin C and 1200mg NAC administered orally on the following day.

Barbanti, 2015 included 112 patients undergoing Transcatheter Aortic Valve Implantation (TAVI) who were randomly assigned to either the controlled diuresis group (n=56) or the control group (intravenous saline solution at a rate of 1 ml/kg/h 12 h before TAVI, during contrast exposure, and for 6 h after the procedure).

Viconti, 2016 describes also a group of patients undergoing TAVI (n=48) with either controlled diuresis or bicarbonate schedule (same schedule as Birguori, 2011). In total, 48 patients were assigned (non-randomly) to the RenalGuard therapy group (n=22) or the control group (n=26). Because the above-mentioned studies used different hydration schemes and methods, the studies could not be pooled.

Brar, 2014 described a slightly different approach: during CAG, a left ventricular catheter was placed in order to measure left ventricular end-diastolic pressure. This was done in 178 patients with eGFR <60 ml/min/1.73m² and one or more additional risk factors, such as diabetes, congestive heart failure, hypertension and age >75 years. The control group consisted of 172 patients with the same characteristics, undergoing the same procedure. Both groups received a bolus infusion, NaCl 0.9%, 3ml/kg/h, 1 hour pre CAG. The control group received the same fluid at the same rate for 4 hours post CAG. The rate of post contrast fluid in the research group, was dependent on the left ventricular end-diastolic pressure: <13mmHg 5ml/kg/h, 13 to 18mmHg 3ml/kg/h and >18mmHg 1.5ml/kg/h.

Another approach, described by Qian, 2016, is invasively measuring central venous pressure (CVP) and CVP-guided fluid administration in 264 patients. CVP <6mmHg 3ml/kg/h, CVP 6-12mmHg 1.5ml/kg/h, CVP >12mmHg 1ml/kg/h NaCl 0.9% 6 hours pre and 12 hours post CM administration. The control group received NaCl 1ml/kg/h 6 hours pre and 12 hours post CM administration. All patients were scheduled for CAG and/or PCI, had an eGFR 15-60 ml/min/1.73m² and LVEF <50% (Qian, 2016).

Results

Briguori, 2011, Marenzi, 2012 and Usmiani, 2015 all reported a significantly lower incidence of PC-AKI in patients who received controlled diuresis. Briguori, 2011 found an incidence of PC-AKI of 11% in the forced diuresis group versus 20.5% in the control group (p=0.025) in patients with an eGFR <30mL/min/1.73m². After 1 month, mortality

was similar in the intervention (6/146) and control (6/146) group, $p=0.99$. A need for dialysis arose in 7/146 patients in the control group versus 1/146 in the intervention group, $p=0.03$.

Marenzi, 2012 found an incidence of PC-AKI of 4,6% in the forced diuresis group versus 18% in the control group ($p=0.005$). In-hospital mortality was similar in the intervention (1/87) and control (2/82) group, $p=0.53$. Need for dialysis arose in 1/87 patients in the intervention group versus 3/83 in the control group, $p=0.29$.

Usmiani, 2016 found an incidence of PC-AKI of 7% in the forced diuresis group versus 25% in the control group ($p=0.01$). One-year mortality was not significantly different in the intervention (4/59) and control (8/65) group, $p=0.46$. Need for dialysis arose in 0/59 patients in the intervention group versus 2/65 in the control group, (p -value not reported).

Barbanti reported that the incidence of CI-AKI was lower in the controlled diuresis group compared to the control group (intravenous), controlled diuresis: 4/56 (5.4%) vs control: 13/56 (13.3%) ($p=0.014$).

Visconti, 2016 reported that PC-AKI occurred in 10/26 (38.5%) patients in the control group and in 1/22 (4.5%) patients in the Renal Guard group ($p=0.005$, odds ratio [OR] 0.076, 95% confidence interval [CI]: 0.009-0.66).

Brar, 2014 described that PC-AKI occurred in 16.3% of the patients in the control group vs. 6.7% in the research group ($p=0.005$). After 6 months, mortality was lower in the intervention (1/196) compared to the control (8/200) group, $p=0.037$. Need for dialysis arose in 1/196 patients in the intervention group versus 4/200 in the control group, $p=0.37$.

Qian, 2016 reported that PC-AKI occurred in 15.9% in the CVP group vs. 29.5% in the standard hydration group ($p=0.006$). Need for dialysis arose in 4/134 patients in the intervention group versus 13/135 in the control group, $p=0.019$. Acute pulmonary oedema occurred in 5/134 patients in the intervention group versus 4/135 in the control group, $p=0.50$. Mortality rates were not reported.

Quality of evidence

For the comparison controlled diuresis versus IV hydration in all patients the level of evidence was graded as low due to imprecision and heterogeneity of included studies.

Figure 6.1 Pooled analysis of PC-AKI risk in patients receiving short schedules of hydration with either bicarbonate or saline for CAG/PCI

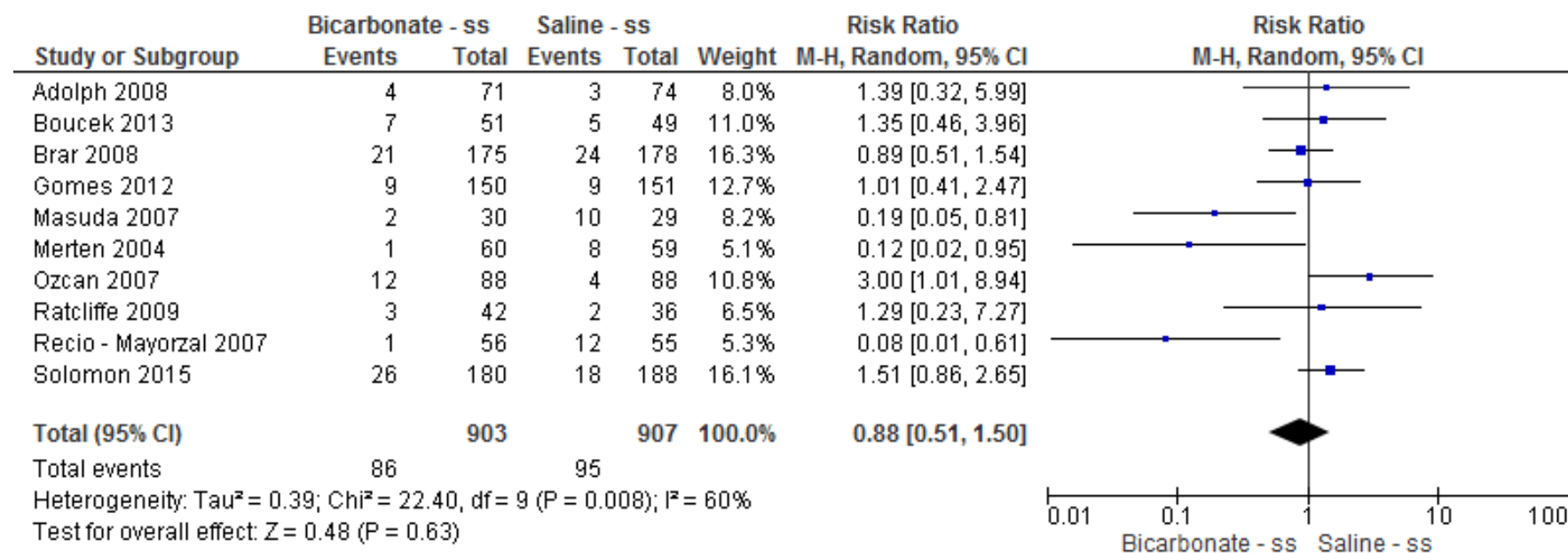


Figure 6.2 Pooled analysis of PC-AKI risk in patients receiving short schedules for bicarbonate versus long schedule for saline for CAG/PCI.

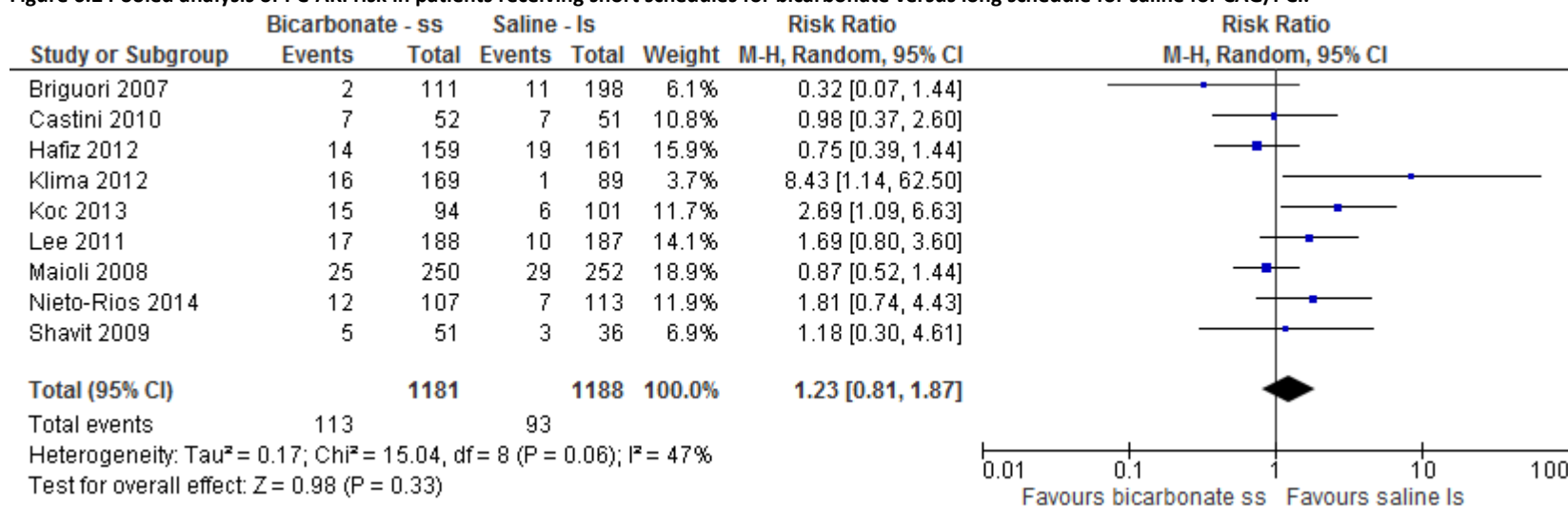


Table 6.3 Adverse events in bicarbonate versus saline infusion or controlled hydration versus standard hydration.

Author and date	Mortality		Dialysis		Heart failure or oedema	
	Bicarbonate	Saline	Bicarbonate	Saline	Bicarbonate	Saline
Patients receiving short schedules of hydration with either bicarbonate or saline for CAG/PCI						
Adolph, 2008	NR	NR	0/71	0/74	NR	NR
Boucek, 2013	0/51	0/49	1/51	2/49	NR	NR
Brar, 2008	4/175	7/178	2/175	4/178	NR	NR
Gomes, 2012	6/150	7/151	NR	NR	NR	NR
Masuda, 2004	NR	NR	NR	NR	NR	NR
Merten, 2004	0/30	2/29	1/30	3/29	11/30	11/29
Ozcan, 2007	NR	NR	1/88	1/88	0/88	0/88
Ratcliffe, 2009	0/42	0/36	0/42	0/36	0/42	0/36
Recio-Mayoral, 2007	1/180	4/188	1/180	3/186	1/180	2/188
Solomon, 2015						
Total	11/658	20/631	6/637	13/640	12/340	13/341
Patients receiving short schedules for bicarbonate versus long schedule for saline for CAG/PCI						
Briguori, 2007	NR	NR	1/108	1/111	NR	NR
Castini, 2010	NR	NR	0/52	0/51	NR	NR
Hafiz, 2012	0/159	0/151	0/159	0/151	0/159	0/151
Klima, 2011	0/169	0/89	0/169	0/89	0/169	0/89
Koc, 2013	NR	NR	NR	NR	NR	NR
Lee, 2011	6/193	2/189	10/193	3/189	0/193	0/189
Maioli, 2008	4/250	3/252	1/250	1/252	NR	NR
Nieto-Rios, 2014	NR	NR	NR	NR	8/103	7/113
Shavit, 2009	NR	NR	0/51	0/36	NR	NR
Total	12/927	5/838	12/982	5/879	8/624	7/542
Patients receiving bicarbonate or saline hydration in "other" hydration schemes for coronary angiography						
Chong, 2015	NR	NR	0/157	1/153	NR	NR
Motohiro, 2011	NR	NR	0/78	0/77	0/78	0/77
Tamuro, 2009	NR	NR	0/72	1/72	0/72	0/72
Ueda, 2011	2/30	3/29	0/30	0/29	0/30	0/29
Patients receiving controlled hydration						
	C.H.	Control	C.H.	Control	C.H.	Control
Barbanti, 2015	1/56	2/56	0/56	0/56	NR	NR
Brar, 2014	1/196	4/200	1/196	8/200	NR	NR
Briguori, 2011	NR	NR	1/146	6/146	NR	NR
Marenzi, 2012	1/87	2/83	1/87	3/93	5/87	10/83
Qian, 2016	4/134	13/135	NR	NR	5/134	4/135
Usmiani, 2016	4/59	8/65	0/59	2/65	NR	NR

Visconti, 2016	NR	NR	0/22	2/26	NR	NR
Total	11/532	29/539	3/566	21/586	10/221	14/218

C.H.: controlled hydration; NR: not reported

Conclusions

<p>Low GRADE</p>	<p>There is a low level of evidence that withholding hydration is as effective as single bolus hydration of 250ml NaHCO₃ in the prevention of PC-AKI prior to computed tomography pulmonary angiography with intravenous iodine-containing CM administration for suspected pulmonary embolism.</p> <p><i>(Kooiman, 2014)</i></p>
<p>Moderate GRADE</p>	<p>There is a moderate level of evidence that no hydration is non-inferior in preventing PC-AKI compared with intravenous pre- and post- hydration in patients with an eGFR between 30-59 ml/min/1.73m².</p> <p><i>(Nijssen, 2017)</i></p>
<p>Low GRADE</p>	<p>There is a low level of evidence that oral hydration is as effective as intravenous hydration in the prevention of PC-AKI in patients receiving intra-arterial iodine-containing contrast medium administration.</p> <p><i>(Cho, 2010)</i></p>
	<p>No evidence was found regarding the effectiveness of oral hydration versus intravenous hydration in the prevention of PC-AKI in patients receiving intravenous iodine-containing contrast medium.</p>
<p>Low GRADE</p>	<p>Bicarbonate and saline pre- and post-hydration are similar in the prevention of PC-AKI independent on the administered schedules.</p> <p><i>(Adolph, 2008; Boucek, 2013; Brar, 2008; Briguori, 2007; Castini, 2010; Chong, 2014; Gomes, 2012; Hafiz, 2012; Klima, 2011; Koc, 2013; Lee, 2011; Maioli, 2008; Masuda, 2007; Merten, 2004; Nieto Rios, 2014; Ozcan, 2007; Ratcliffe, 2009; Recio-Mayoral, 2007; Shavit, 2009; Solomon, 2015)</i></p>
<p>Moderate GRADE</p>	<p>There is a moderate level of evidence that administration of 250ml NaHCO₃ 1.4% prehydration is as effective as 1000ml NaCl 0.9% prehydration and 1000ml NaCl 0.9% posthydration in the prevention of PC-AKI in CT.</p> <p><i>(Kooiman, 2014)</i></p>
<p>Low GRADE</p>	<p>There is a low level of evidence that hydration with controlled diuresis is more effective than intravenous hydration alone in the prevention of PC-AKI in patients who underwent cardioangiography procedures with intra-arterial iodine-containing contrast medium administration.</p> <p><i>(Barbanti, 2015; Brar, 2014; Briguori, 2011; Marenzi, 2012; Qian, 2016; Usmiani, 2016; Visconti 2016)</i></p>
	<p>No evidence was found regarding the effectiveness of hydration with controlled diuresis versus intravenous hydration in the prevention of PC-AKI in patients who underwent CT with intravenous iodine-containing</p>

Considerations

All studies

The number of patients with eGFR <30 ml/min/1.73m² is absent or very low in all described studies. No RCT has been published focusing on patients with eGFR <30 ml/min/1.73m² only, and subanalyses for this group within other RCTs were not performed. Furthermore, independent of eGFR, all patients receiving CM should have a normal hydration status. Dehydration should be corrected at all times before administering CM.

Hydration versus no hydration

The most valuable new information comes from the study from Nijssen, 2017. This prospective randomised RCT in 603 patients with eGFR 30-59 ml/min/1.73m², shows that the incidence of PC-AKI is the same in the group receiving pre- and post-hydration with NaCl 0.9% compared to the group withholding hydration, 2.7% versus 2.6% respectively (one-sided 95% CI -2.25 to 2.06). Further analyses showed no significant differences in the incidence of PC-AKI between patients receiving iv NaCl 0.9% and those not receiving prophylaxis in the subgroups with or without diabetes; eGFR 30-44 ml/min/1.73m² or eGFR 45-59 ml/min/1.73m²; intra-arterial contrast administration or intra-venous contrast administration; and undergoing an interventional or diagnostic procedure. As this study has been conducted in the Netherlands, these results are highly applicable to this guideline.

Oral versus intravenous hydration

The quality of evidence for the effectivity of oral hydration for the prevention of PC-AKI is low. Furthermore, the oral intake of patients could not be quantified and could therefore lead to PC-AKI due to lack of adherence to oral hydration instructions. Therefore, it is the recommendation of the working group that oral hydration should not be used in the prevention of PC-AKI. However, the encouragement of patients using oral fluids unrestrictedly on the day of CM exposure, besides other preventive measures, is advisable.

Saline versus bicarbonate

Intravenous administration of NaCl 0.9% before, during and after CM administration will produce an infusion rate-dependent increase in tubular fluid volume, reduction in CM intratubular concentration, and slight increases in tubular pH. The lower tubular concentrations of CM lead to reduced formation of reactive oxygen species (ROS) and therefore to reduced toxicity to tubular cells.

Infusion of NaHCO₃ 1.4% has the same effects as NaCl 0.9% infusion with the additional benefit of a substantial increase in the bicarbonate anion buffer throughout the renal tubule. Higher pH is known to decrease cellular apoptosis in the setting of ROS formation. Prehydration with NaHCO₃ will raise the proximal tubular bicarbonate anion and pH levels close to those found in blood. Maintenance of NaHCO₃ infusion will keep the bicarbonate anion levels raised while the CM is excreted. (Burgess, 2014)

For descriptive purposes, three hydration schedules have been described in the literature:

- long schedule: 1ml/kg/h for 12h pre and for 12h post CM administration;
- short schedule: 3ml/kg/h for 1h pre and 1ml/kg/h 6h post CM administration;
- ultra short schedule: 3ml/kg/h NaHCO₃ 1.4% for 1h pre-CM administration (Kooiman, 2014).

The landmark paper giving the first evidence on the effectiveness of NaHCO₃ pre- and post hydration was published in 2004 (Merten, 2004). This group describes an RCT consisting of 119 patients with sCr \geq 97,2 μ mol/l undergoing either cardiac catheterizations (n=97) or CT (n=9) or other procedures involving intravascular contrast administration (n=13). Patients were randomly assigned to receive either 154mEq/l NaHCO₃ or 154mEq/l NaCl, both in dextrose 5% in water. Both groups received the fluid mixture at a rate of 3ml/kg/h for 1 hour pre CM injection and at a rate of 1ml/kg/h for 6 hours after CM injection. PC-AKI was defined as a rise of sCr \geq 25% within 2 days after CM administration. The incidence of PC-AKI in the NaHCO₃ group was 1.7% (1 of 60) and 13.6% (8 of 59) in the NaCl group.

The positive results of this relatively short NaHCO₃ hydration schedule triggered a boom in RCTs comparing NaHCO₃ vs. NaCl. The mixture used in the landmark paper is not commercially available. The most resembling commercially available concentrations are NaHCO₃ 1.4% (i.e. 166 mEq/L NaHCO₃) and NaCl 0,9%. Some RCTs used the commercially available solutions, others used the mixture described by Merten (2004).

Many studies are now available comparing the effect of bicarbonate hydration to saline hydration on the risk of PC-AKI. However, these studies are very heterogeneous in the hydration solutions, volumes and schedules. Also, sample size is often small and confidence intervals are wide, also due to the low incidence of PC-AKI. Therefore, the conclusions on the comparison of bicarbonate and saline in terms of prevention of CI-AKI are not certain, but overall, no difference in PC-AKI risk is found. Also, when considering the literature results, no preference can be given for a certain hydration schedule.

Since bicarbonate can be given just 1 hour prior to CM administration and thus considered more patient friendly and less burdensome on the healthcare system, the Working Group expresses a preference for this type of bicarbonate hydration.

The literature on effectiveness of hydration schedules for prevention of PC-AKI would greatly benefit from optimized study designs with properly defined control populations (e.g. supported by propensity score matching) as has been done for PC-AKI risk stratification studies when CM is injected intravenously or for hydration in CT pulmonary angiography.

Although the bicarbonate prehydration volume is relatively low, the risk of pulmonary fluid overload or congestive heart failure should be considered and weighed against its potential benefit, especially in patients on chronic dialysis and with poor cardiac function and critical illness related fluid overload.

Note: In critically ill patients lactated Ringer's, a balanced crystalloid, may be preferable to saline hydration because of its somewhat lower osmolality and the reduced chance of hyperchloraemic acidosis, which may contribute to the preservation of renal function.

Hydration with controlled diuresis

The ratio behind this technique is to increase renal blood flow and urinary output in a controlled environment, based on patient's parameters, such as central venous pressure, left ventricular end diastolic pressure or urinary output. The amount of additional intravenous fluids and if necessary low dose diuretics is individualized by the abovementioned parameters. These techniques can only be applied in an in-patient setting, as intravenous or intra-arterial catheters are necessary, combined with a urinary catheter for monitoring urinary production. This makes these techniques applicable for a subgroup of patients. The Working Group thinks that controlled diuresis is a promising new invasive strategy to prevent PC-AKI in hospitalized patients undergoing (cardiac) angiography with or without intervention. Which technique is optimal is unknown. More information and research is needed before reliable conclusions can be drawn regarding the effectiveness and preferred type of controlled diuresis, or its application in an outpatient setting. Therefore, the Working Group recommends that, for now, this technique should be reserved for a research setting only.

Recommendation

For patients with an eGFR <30 ml/min/1.73m² undergoing intravascular administration of iodine-containing contrast medium either one of the following options can be used:

- prehydrate with 250ml (or 3ml/kg/h) NaHCO₃ 1.4% in 1h pre-CM administration;
- pre- and posthydrate with 250ml (or 3ml/kg/h) NaHCO₃ 1.4% in 1h pre-CM and 500ml (or 1ml/kg/h) in 6h post-CM administration.

Do not use hydration with controlled diuresis for the prevention of PC-AKI in patients undergoing (cardiac) angiography with or without intervention, unless it is performed in a research setting.

Do not use oral hydration as the sole means of prevention of PC-AKI.

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Chapter 7 Other Preventive Measures

Questions

- 7.1 Should Statins in addition to hydration be recommended to reduce the incidence of PC-AKI in patients with pre-existent reduced kidney function receiving intravascular iodine-containing contrast medium?
- 7.2 Should prophylactic N-acetylcysteine (NAC) in addition to hydration be recommended to reduce the incidence of PC-AKI in patients receiving intravascular contrast?
- 7.3 Should prophylactic Vitamin C in addition to hydration be recommended to reduce the incidence of PC-AKI in patients with pre-existent reduced kidney function receiving intravascular contrast medium?
- 7.4 Should medication be discontinued prior to intravascular contrast medium administration to reduce the risk of PC-AKI?
- 7.5 Should prophylactic renal replacement therapy be recommended to reduce the risk of PC-AKI in patients with CKD stage 4 to 5 receiving intravascular contrast medium?

Sub questions

- 7.2.1 Should prophylactic N-acetylcysteine in addition to hydration be recommended to reduce the incidence of PC-AKI in patients with reduced kidney function (eGFR <60 ml/min/1.73m²) receiving intravascular contrast?
- 7.5.1 Should the dialysis schedule be adapted when a CKD stage-5 patient receives intravascular contrast medium?

7.1 Should Statins in addition to hydration be recommended to reduce the incidence of PC-AKI in patients with pre-existent reduced kidney function receiving intravascular contrast medium?

Introduction

Statins are primarily used in cardiovascular medicine for their lipid lowering effects. In addition to their impact on cholesterol, statins are known to have multiple non-lipid inhibiting effects on endothelial function, inflammation responses, oxidative stress and apoptotic pathways. The pathophysiology of PC-AKI is not completely understood, but may in part be due to high oxidative stress, inflammation and vasoconstriction. Therefore, statins may be beneficial for the prevention of PC-AKI. Clinical studies with statins to prevent PC-AKI have shown conflicting results, but there seems to be a beneficial effect in patients undergoing coronary angiography or percutaneous coronary intervention (PCI), especially in the setting of an acute coronary syndrome.

Literature search and selection

To answer our clinical question a systematic literature analysis was performed for the following research question:

Can statins when compared to no statins reduce the incidence of PC-AKI in patients with pre-existent reduced kidney function receiving intravascular contrast?

P (patient category)	patients undergoing radiological examinations with reduced kidney function receiving intravascular contrast;
I (intervention)	statins in combination with hydration;
C (comparison)	hydration alone or no preventive measures;
O (outcome)	PC-AKI, start dialysis, mortality, intensive care admission.

Relevant outcome measures

The working group considered PC-AKI, mortality and start dialysis critical outcome measures for the decision making process and the intensive care admission important outcome measures for the decision-making process.

A difference of at least 10% in relative risk was defined as a clinically relevant difference, by expert opinion of the working group (no literature was available to substantiate the decision). To illustrate, if PC-AKI occurs with an incidence of 10% in the patient population, a difference of 10% of relative risk would mean a difference of 1% in absolute risk. Thus the number needed to treat would be 100, ergo: a doctor would need to treat 100 patients to prevent one case of PC-AKI. When the incidence of PC-AKI is 5%, a difference of 10% in relative risk would mean a difference of 0.5% in absolute risk, and a number needed to treat of 200.

Search and select (method)

The data bases Medline (OVID) and Embase were searched from January 1995 to 12 Augustus 2015 using relevant search terms for systematic reviews (SRs) and randomized controlled trials (RCTs). This search was updated on 1 May 2017.

A total of 174 studies were found. The initial literature search produced 131 hits and the update produced 43 hits. The following inclusion criteria were applied:

- randomized controlled trial or meta-analysis;
- adult patients who underwent radiological examination using intravascular contrast media;
- patients with impaired kidney function, at least eGFR < 60ml/min/1.73m²;
- hydration types: hydration with i.v. NaCl or bicarbonate, oral hydration;
- the intervention arm consisted of patients that received statins and hydration. All types of statins and statin protocols included;
- the control arm consisted of patients that received hydration only or no preventive measures;
- studies that provided N-acetylcysteine (NAC) were included, when both groups received the same doses;
- at least one of the outcome measures was described: PC-AKI, start dialysis, mortality, and intensive care admission.

Based on title and abstract 74 studies were selected. After examination of full text, 71 studies were excluded and one study was added after cross-referencing, leaving 4 studies to be included in the literature summary. Reasons for exclusion are described in the exclusion table.

Results

Four studies were included in the literature analysis, one meta-analysis and three randomized controlled studies. The most important study characteristics and results are included in the evidence tables.

Summary of literature

Description of studies

Risk of PC-AKI

Table 7.1 presents the characteristics of the included studies. The systematic review and meta-analysis of Liu, 2015 evaluated the protective effects of statins on PC-AKI, renal replacement therapy and mortality in patients undergoing coronary angiography/percutaneous intervention. Here we encompassed only the 6 RCTs (n=1684) that were included in the subgroup analysis that focused on patients with renal dysfunction. The intervention protocol differed across studies (table). In 3 of the 6 studies both patients in the intervention as the control group were given N-acetylcysteine. The definition of PC-AKI varied (table). Where possible, the definition of PC-AKI as described in the introduction of the guideline was used to interpret the results.

As Liu, 2015 did not include specific subgroup analyses including patients with renal dysfunction for the outcomes renal replacement therapy and all-cause death; the data of the original articles were included.

Abaci, 2015 was a RCT exploring the efficacy of high-dose rosuvastatin in decreasing the incidence of PC-AKI in statin-naive patients with an eGFR between 30 and 60mL/min/1.73m² the day before elective coronary angiography. 208 patients completed the study. Patients in the intervention group were given 40mg rosuvastatin <24h before the procedure and 20mg/day for the 2 days hereafter. Patients in the control group did not get statins. All patients received intravenous hydration. The primary outcome measure was the incidence of PC-AKI, defined as a rise of ≥25% or ≥0.5mg/dl in serum creatinine from baseline, <48 or 72 hours after contrast exposure.

In the RCTs of Shehata, 2015 and Qiao, 2015, a total of 250 diabetic patients with mild to moderate chronic kidney diseases were included. The participants in the intervention group in the study of Shehata, 2015 received oral atorvastatin (80mg daily for 48h) before PCI. Qiao, 2015 treated the intervention group with rosuvastatin (10 mg everyday for at least 48 hours before and 72 hours after CM administration for PCI). Shehata, 2015 provided both the intervention and control group in addition to periprocedural intravenous infusion of isotonic saline with oral N-acetylcysteine.

No studies were found where statins were compared to a control group in terms of PC-AKI, in patients undergoing computed tomography with intravenous CM administration.

Table 7.1 Description of the study population, definition of PC-AKI, type and dose of the statins used, type of hydration and incidence of PC-AKI

	Inclusion	Definition PC-AKI	Type and dose of statin	Normal saline iv hydration	Incidence statins (%)	Incidence Control (%)
Jo, 2008	CrCl≤60 mL/min or SCr ≥ 1.1 mg/dL Only patients who did not recently (<30 days before procedure) used statins and undergoing coronary angiography were included.	A relative increase in baseline SCr of ≥25% and/or an absolute increase of ≥0.5 mg/dL within 48h after contrast administration	Simvastatin 40mg every 12h for 2 days, in total 80 mg before procedure and 80 mg after the procedure, starting the evening of the day of the procedure.	Half-isotonic saline, 1 L/kg/h 12h before and after the procedure.	PC-AKI: 2.5 Mortality: 0 Start dialysis: 0 ICU admission: NR	PC-AKI: 3.4 Mortality: 0 Start dialysis: 1 ICU admission: NR
Toso, 2010	CrCL<60 mL/min Patients without current statin treatment who underwent elective coronary angiography and/or other intervention.	Primary: absolute serum creatinine increase of ≥0.5 mg/dL over baseline within 5 days after the admission of contrast medium. Secondary: a relative increase of ≥25% over baseline within 5 days.	Atorvastatin 80 mg/d for 48h before and after the procedure. All patients received oral NAC 1200mg twice a day from the day before to the day after procedure.	Isotonic saline, 1 mL/kg/h, 0.9% sodium chloride 12h before and after the procedure.	PC-AKI: primary 10/secondary: 17 Mortality: 1 Start dialysis: 0 ICU admission: NR	PC-AKI: primary 11/secondary: 15 Mortality: 0 Start dialysis: 1 ICU admission: NR
Patti, 2011	Scr≤3mg/dL, subgroup with pre-existing renal failure: serum creatinine level ≥1.5mg/dl or CrCl≤60. Statin-naïve patients (patients with statin treatment <3 months were excluded) with acute coronary syndrome undergoing percutaneous coronary intervention.	Increase in serum creatinine ≥0.5mg/dL or >25% from baseline at 24h or 48h after PCI.	Atorvastatin 80 mg 12h before and 40 mg 2 hours before angiography. All patients received atorvastatin 40mg/day after PCI.	For patients with preprocedural serum creatinine level ≥1.5mg/dl or CrCl≤60: saline, 1mL/kg/h for ≥12h before and ≥24h after procedure.	PC-AKI: 14.3 Mortality: NR Start dialysis: NR ICU admission: NR	PC-AKI: 25.6 Mortality: NR Start dialysis: NR ICU admission: NR
Quintavalle, 2012	eGRF≤60mL/min/1.73m ² Naïve patients scheduled for elective coronary angiography or percutaneous coronary intervention.	Three different definitions are used. Here, we choose to include the results associated an increase of sCr concentration ≥25% at 48 hours from baseline	Atorvastatin 80mg within 24h before procedure. All patients received oral NAC 1200mg twice, a day before and the day of the procedure.	Sodium bicarbonate, 3mL/kg/h for 1 hour before contrast injection, 1 mL/kg/h during and for 6 hours after the procedure.	PC-AKI: 3 Mortality: NR Start dialysis: NR ICU admission: NR	PC-AKI: 7 Mortality: NR Start dialysis: NR ICU admission: NR
Han, 2014	30≤eGRF≤90	Increase in sCR	Rosuvastin 10 mg/day	Isotonic saline, 0.9%	PC-AKI: 3.6	PC-AKI: 4.4

	Inclusion	Definition PC-AKI	Type and dose of statin	Normal saline iv hydration	Incidence statins (%)	Incidence Control (%)
	<p>mL/min/1.73m². Here only the results of patients with eGFR≤60 mL/min/1.73m² were included.</p> <p>Only type 2 DM patients who did not received any statin treatment for at least 14 days who were undergoing coronary/peripheral arterial diagnostic angiography, left ventriculography or percutaneous coronary intervention were included.</p>	concentration ≥0.5 mg/dL or ≥25% above baseline at 72h after exposure.	from 2 days before to 3 days after procedure.	sodium chloride, 1mL/kg/h started 12h before and continued for 24h after the procedure.	Mortality: NR Start dialysis: NR ICU admission: NR	Mortality: NR Start dialysis: NR ICU admission: NR
Leoncini, 2014	<p>sCr≤3mg/dL or without acute renal failure or renal replacement therapy. Here the results of a subgroup with eCrCL<60mL/min are presented.</p> <p>Statin-naïve patients with acute coronary syndrome undergoing early invasive strategy.</p>	Primary: increase in sCr concentration ≥0.5 mg/dL or ≥25% above baseline at 72h after exposure.	Rosuvastatin 40mg and 20mg/d. At discharge patients continued treatment (20mg/d), while patients in the control group received 40 mg/day atorvastatin. All patients received oral NAC 1200 mg twice a day from the day before through the day after procedure	0.9% Sodium chloride, 1 mL/kg/h for 12h before and after procedure.	PC-AKI: 8.6 Mortality: NR Start dialysis: NR ICU admission: NR	PC-AKI: 21.0 Mortality: NR Start dialysis: NR ICU admission: NR
Abaci, 2015	<p>eGFR 30-60mL/min/1.73m²</p> <p>Patients were naïve to statins and scheduled for elective coronary angiography</p>	Increase in serum creatinine of ≥0.5 mg/dL or ≥25% from baseline <48 or 72 hours after angiography.	Rosuvastatin 40mg <24h before procedure and then 20mg/day for 2 days.	Isotonic saline, 1mL/kg/h, 0.9% sodium chloride for 12h before and 24h after procedure.	PC-AKI: 5.8 Mortality: NR Start dialysis: NR ICU admission: NR	PC-AKI: 8.6 Mortality: NR Start dialysis: NR ICU admission: NR
Shehata, 2015	Diabetic patients, carrying the diagnosis of chronic stable angina and suffering from mild or moderate	Increase in serum creatinine by >0.5 mg/dL (44.2 μmol/L) or >25% of baseline value	Oral atorvastatin (80 mg daily) for 48 h before PCI, in addition to periprocedural intravenous	Intravenous infusion of isotonic saline and oral N-acetylcysteine, in addition to placebo formula.	PC-AKI: 7.7 Mortality: NR Start dialysis: 0 ICU admission: NR	PC-AKI: 20 Mortality: NR Start dialysis: 0 ICU admission: NR

	Inclusion	Definition PC-AKI	Type and dose of statin	Normal saline iv hydration	Incidence statins (%)	Incidence Control (%)
	CKD. (eGFR 30– <90 mL/min/1.73 m		infusion of isotonic saline and oral N-acetylcysteine. Standard parenteral hydration protocol in both groups.			
Qiao, 2015	1. Diabetic patients; 2. Mild to moderate CKD, which was defined as estimated glomerular filtration rate (eGFR) 30 to 89 ml/min/1.73m ² ; 3. Total CM administrated dose of volume ≥ 100 ml.	Relative increase in baseline SCr of ≥ 25% and/or an absolute increase of ≥ 0.5 mg/dL (44.2 μmmol/L) within 72 hours after contrast administration	The rosuvastatin group received 10 mg everyday for at least 48 hours before and 72 hours after CM administration.	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).	PC-AKI: 3 Mortality: NR Start dialysis: 0 ICU admission: 0	PC-AKI: 3 Mortality: NR Start dialysis: 0 ICU admission: 0

Results

Risk on PC-AKI

Pooled results of Liu (2015) showed that statin pretreatment significantly decreased the risk of PC-AKI compared to placebo treatment: risk ratio 0.51 (95% CI: 0.37 to 0.70), fixed effects model. However, this meta-analysis might have overestimated the effects of statins, as the results of one study (Quintavalle, 2012) in which PC-AKI was primarily defined as an increase CysC concentration of 10% above the baseline value at 24h after administration of contrast were included.

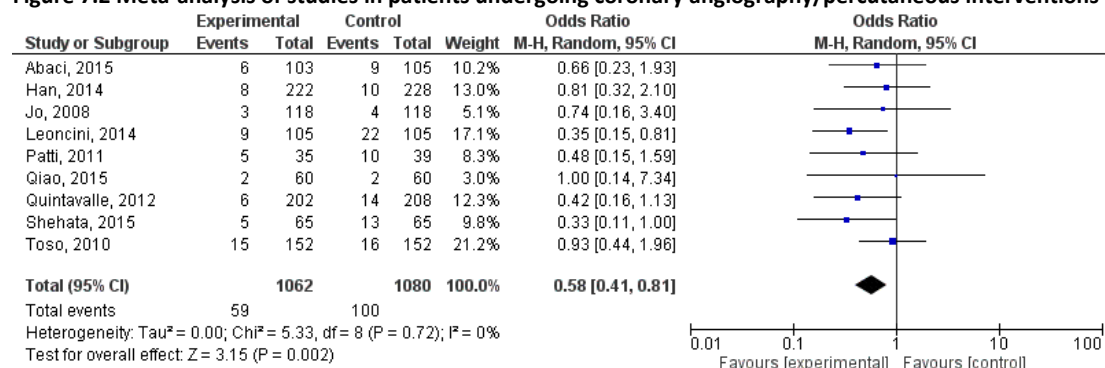
Abaci (2015) reported that 6 of the 103 patients in de rosuvastatin group and 9 of the 105 patients in the control group developed PC-AKI after the procedure.

Meta-analysis

The six studies from the subgroup analysis of Liu, 2015 (adapted results for Quintavalle, 2012) and the studies of Abaci, 2015, Shehata, 2015 and Qiao, 2015 were pooled (Figure 7.2).

Statins significantly decreased the risk of PC-AKI: risk ratio 0.58 (95% CI: 0.41; 0.81, $p=0.002$, random effects model) in patients undergoing coronary angiography/percutaneous interventions.

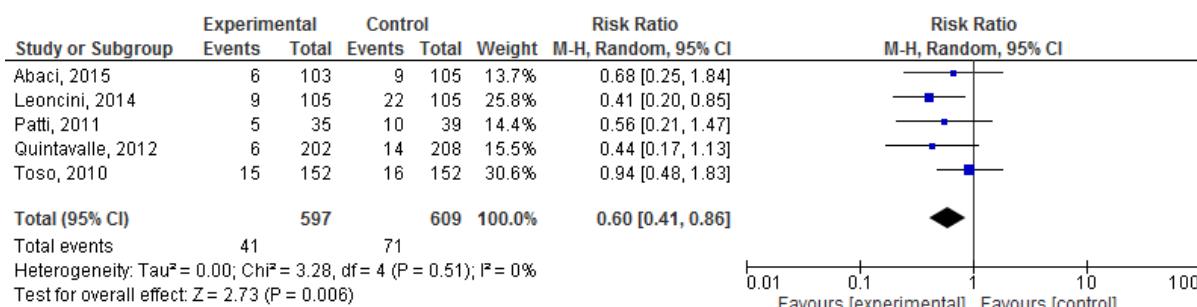
Figure 7.2 Meta-analysis of studies in patients undergoing coronary angiography/percutaneous interventions



A separate meta-analysis (Figure 7.3) was performed to determine the effects of high dose rosuvastatin or atorvastatin on the risk of PC-AKI.

High dose rosuvastatin or atorvastatin significantly decreased the risk of PC-AKI: risk ratio 0.60 (95% CI: 0.41; 0.86, $p=0.006$, random effects model) in patients undergoing coronary angiography/percutaneous interventions.

Figure 7.3 Meta-analysis of studies that evaluated the effects of high dose rosuvastatin or atorvastatin on risk of PC-AKI in patients undergoing coronary angiography/percutaneous interventions



Start dialysis

In the study of Jo (2008) one patient in the placebo group needed haemodialysis for renal failure 3 days after coronary angiography. Toso (2010) reported one case of temporally hemofiltration in the placebo group. In five studies (Abaci, 2015; Han, 2014; Leoncini, 2014; Patti, 2011; Quintavalle, 2012) there were no patients with a need of dialysis, the studies did not report on this outcome, did not provide the results for this specific subgroup of patients (impaired kidney function) or did not report the results for the control and intervention group separately. Thus, in the studies that examined start of dialysis, 0/270 patients in the statin group versus 2/270 in the control group developed need of dialysis after CAG. None of the included studies were powered to detect differences in the outcome start of dialysis and the incidence of this outcome was very low. Because this very low number of cases, no conclusions can be drawn for this outcome.

Mortality

Only Toso (2010) reported one death; one patient in the atorvastatin group died from acute heart failure aggravated by major bleeding. Six studies (Abaci, 2015; Han, 2014; Leoncini, 2014; Patti, 2011; Quintavalle, 2012) did not report on this outcome, reported zero mortality, did not provide the results for this specific subgroup of patients (impaired kidney function) or did not report the results for the control and intervention group separately. None of the included studies were powered to detect differences in the outcome start of dialysis and the incidence of this outcome was very low. Because of the very low number of cases, no conclusions can be drawn for this outcome.

Intensive care admission

The included studies did not report on this outcome measure.

Quality of evidence

The level of quality of evidence for the outcome PC-AKI was decreased from level high to level low due to heterogeneity in statin types and protocol and imprecision (total number of events <300 per group).

For the outcomes start dialysis and mortality, the level of evidence was decreased from high to very low, 1 point for heterogeneity and 2 points for gross imprecision.

Conclusions

Low GRADE	There is evidence of low quality that short-term high dose rosuvastatin or atorvastatin in addition to hydration is more effective than hydration alone in the prevention of PC-AKI in statin-naive patients with eGFR <60 ml/min/1.73m ² undergoing coronary angiography or percutaneous
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	coronary intervention. <i>(Liu, 2015)</i>
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	The effects of statins on mortality, start of dialysis and number of ICU admissions are uncertain in statin-naïve patients with impaired kidney function undergoing coronary angiography or percutaneous coronary intervention.
	No studies were found evaluating the effects of statins on PC-AKI in patients receiving intravenous contrast administration.
	No studies were found evaluating the effects of short-term high dose statins on PC-AKI in patients already receiving chronic low dose statin therapy.
	It is unclear whether increasing the dosage of statin prior to an iodinated CM administration in non-statin-naïve patients reduces the risk of PC-AKI.

Considerations

Patients with reduced renal function have a higher chance to develop PC-AKI. There have been multiple randomized clinical trials performed to evaluate the efficacy of statin pretreatment with conflicting results. The results of this meta-analysis strongly support the benefit of pretreatment with high doses of atorvastatin and rosuvastatin in patients with impaired renal function undergoing coronary angiography or percutaneous coronary intervention (PCI). Since most of the included trials have excluded patients with a GFR $<30\text{ml}/\text{min}/1.73\text{m}^2$, it remains unclear whether statins will be beneficial in patients with chronic kidney disease stage 4 or 5. Uncertainty remains about the timing and duration of pretreatment. Furthermore, the additional effect of temporarily increasing the dosage of statin for a planned procedure in chronic statin using patients is unknown. No studies are available that examined the role of pretreatment with statins for prevention of PC-AKI during administration of intravenous contrast or during percutaneous replacement of aortic valves (TAVR) or placement of a left ventricular pacemaker lead (resynchronization therapy).

In conclusion, atorvastatin and rosuvastatin, when administered at high doses and before iodine-containing contrast administration in statin-naïve patients with reduced renal function undergoing coronary angiography or percutaneous coronary intervention (PCI), have a beneficial effect on the prevention of PC-AKI.

Recommendation

Consider giving short-term (48 hours) high dose atorvastatin or rosuvastatin in addition to hydration in statin-naïve patients with $\text{eGFR} <60\text{ ml}/\text{min}/1.73\text{m}^2$ undergoing coronary angiography with or without percutaneous coronary intervention.

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7.2 Should prophylactic N-acetylcysteine (NAC) in addition to hydration be recommended to reduce the incidence of PC-AKI in patients receiving intravascular iodine-containing contrast medium?

Introduction

The mechanism of PC-AKI is not completely understood. Direct cell damage by the iodine-containing contrast medium with subsequent oxidative stress, endothelial dysfunction and decreased nitric oxide (NO) availability is supposed to play major role. Intrarenal NO is crucial for maintaining perfusion and oxygen supply in the renal medulla. NO depletion causes vasoconstriction with hypoperfusion of the renal medulla and local hypoxia. In addition, NO depletion affects tubular fluid composition, tubule-glomerular feedback signalling and decreases glomerular filtration rate (Liu, 2014).

However, some experts have questioned whether acute kidney injury occurring after intravascular administration of iodine-containing CM is not caused by co-existing risk factors and only coincidentally related to the CM especially if contrast media are administered by the intravenous route. In a meta-analysis of controlled studies the incidence of acute kidney injury was similar between patients receiving IV contrast and patients receiving an imaging procedure without contrast media (McDonald, 2013).

In addition, it is also difficult to distinguish the effects of contrast media from the effects of physiologic confounders that could either elevate or reduce serum creatinine in patients undergoing radiologic studies (Hofmann, 2004; Krasuski, 2003).

There is also a possibility that the effectiveness of NAC could vary by type of iodine-containing contrast medium used, LOCM vs. IOCM.

A recent analysis did not demonstrate a clear benefit of NAC for patients receiving IV contrast media (Subramaniam, 2016). The same analysis found no association between the effect of NAC on the incidence of PC-AKI and mean baseline serum creatinine levels.

The argument for NAC in the decision making process has always been the low risk, the low costs and general availability of the NAC intervention. However, the low costs of NAC itself is offset by extra handling time and a more complex AKI preventive protocol, which are also confounding factors.

Thus, it is unclear whether NAC-administration should be recommended to prevent PC-AKI.

Literature search and selection

To answer our clinical question a systematic literature analysis was performed for the following research question:

Can prophylactic N-acetylcysteine in addition to hydration reduce the incidence of CI-AKI in patients receiving intravascular contrast?

Sub question:

Can prophylactic N-acetylcysteine in addition to hydration reduce the incidence of CI-AKI in patients receiving intravascular contrast in certain subgroups of patient (For example, patients with reduced kidney function)?

P (patient category) adult patients undergoing radiological examinations receiving intravascular contrast;
I (intervention) N-acetylcysteine acid in combination with hydration, N-acetylcysteine alone;
C (comparison) hydration alone, no preventive measures;
O (outcome) post-contrast acute kidney injury (PC-AKI), start dialysis, decrease in residual kidney function, adverse effects of hydration (overfilling, intensive care unit admittance, mortality), cost-effectiveness.

Relevant outcome measures

The working group considered PC-AKI, mortality and start dialysis critical outcome measures for the decision making process and the intensive care admission important outcome measures for the decision-making process.

A difference of at least 10% in relative risk was defined as a clinically relevant difference, by expert opinion of the working group (no literature was available to substantiate the decision). To illustrate, if PC-AKI occurs with an incidence of 10% in the patient population, a difference of 10% of relative risk would mean a difference of 1% in absolute risk. Thus the number needed to treat would be 100, ergo: a doctor would need to treat 100 patients to prevent one case of PC-AKI. When the incidence of PC-AKI is 5%, a difference of 10% in relative risk would mean a difference of 0.5% in absolute risk, and a number needed to treat of 200.

Search and select (method)

The databases Medline (OVID), Embase and the Cochrane Library were searched from January 2005 to 23rd of July 2015 using relevant search terms for systematic reviews (SRs) and randomized controlled trials (RCTs). This search was updated on 1 May 2017.

A total of 341 studies were found. The initial literature search produced 302 hits and the update produced 39 hits. The following search criteria were applied:

- adult patients who underwent radiological examination using intravascular iodine-containing contrast media (including radiological examination during percutaneous angiography);
- patients with impaired kidney function, at least eGFR $<60 \text{ ml/min}1.73\text{m}^2$ were analysed separately from those with a normal kidney function
- hydration types: hydration with NaCl, hydration with bicarbonate, oral hydration, pre-hydration, pre- and posthydration;
- N-acetylcysteine that was administered in one of the treatment arms;
- the control arm consisted of patients that received hydration or no hydration;
- at least one of the outcome measures was described: Contrast-induced nephropathy (CIN) / contrast-induced acute kidney injury (CI-AKI), start dialysis, decrease in residual kidney function, adverse effects of hydration (overfilling, intensive care unit admittance, mortality), cost-effectiveness.

Based on title and abstract a total of 91 studies were selected. After examination of full texts a total of 67 studies were excluded and 24 studies definitely included in the literature summary. Reasons for exclusion are described in the exclusion table. During the search update, no more papers were included that described patients with a normal kidney function ($\text{eGFR} \geq 60 \text{ ml/min}1.73\text{m}^2$). The reason for this was that the working group decided to focus the recommendations on patients with an impaired eGFR ($<60 \text{ ml/min}1.73\text{m}^2$) only, because in regular clinical practice no one will consider inserting the administration of NAC in the study protocol in the population with a normal kidney function ($\text{eGFR} \geq 60 \text{ ml/min}1.73\text{m}^2$).

Results

24 studies were included in the literature analysis; the most important study characteristics and results were included in the evidence tables. The evidence tables and assessment of individual study quality are included.

Summary of literature

Description of studies

CT scan, normal kidney function

One RCT (Hsu, 2012) reported on effects of NAC plus saline hydration (n=106) versus saline hydration only (n=103) in terms of incidence of PC-AKI in patients undergoing CT-scans with intravascular contrast medium. NAC was administered intravenously (600mg) prior to the CT-scan.

CT scan, decreased kidney function

A total of 5 RCTs (Kama, 2014; Kitzler, 2012; Poletti, 2007; Poletti, 2013; Tepel, 2000) with 386 patients was included. Three studies described emergency patients (Kama, 2014; Poletti, 2007; Poletti, 2013) while two studies described elective patients (Kitzler, 2012; Tepel, 2000). In two RCTs the N-acetylcysteine was administered orally (Kitzler, 2014; Tepel, 2000), with the total doses varying between 2.4g and 4.8g. In three RCTs the N-acetylcysteine was administered intravenously (Kama, 2014; Poletti, 2007; Poletti, 2013) with total doses varying between 1.05 g (150mg/kg) and 6g. The follow-up time in the studies varied between 3 days and 10 days (for laboratory parameters).

Coronary angiography and/or percutaneous intervention, normal kidney function

A total of 8 RCTs was included (Carbonell, 2007; Jaffrey, 2012; Kim, 2010; Kinbara, 2010; Lawlor, 2007; Sadat, 2011; Tanaka, 2011; Thiele, 2010) with 3093 patients was included. Four studies described emergency patients (Carbonell, 2007; Jaffrey, 2012; Tanaka, 2011; Thiele, 2010) while four studies described elective patients (Kim, 2010; Kinbara, 2010; Lawlor, 2007; Sadat, 2011;). In four RCTs the N-acetylcysteine was administered orally (Kim, 2010; Kinbara, 2010; Sadat, 2011; Tanaka, 2011), with the total doses varying between 2.4g and 2.8g. In four RCTs the N-acetylcysteine was administered intravenously (Carbonell, 2007; Jaffrey, 2012; Lawlor, 2007; Thiele, 2010) with total doses varying between 1g and 6g. The follow-up time in the studies varied between 2 days and 7 days (for laboratory parameters).

Coronary angiography and/or percutaneous intervention, impaired kidney function

A total of 10 RCTs was included (ACT, 2011; Castini, 2010; Ferrario, 2009; Gulel, 2005; Habib, 2016; Izani Wan, 2008; Koc, 2012; Kotlyar, 2005; Sadineni, 2017; Seyon, 2007)

with 1188 patients was included. One study described emergency patients (Seyon, 2007) while 7 studies described elective patients (ACT, 2011; Castini, 2010; Ferrario, 2009; Gulel, 2005; Izani Wan, 2008; Koc, 2012; Kotlyar, 2005). In 6 RCTs the N-acetylcysteine was administered orally (ACT, 2011; Castini, 2010; Ferrario, 2009; Gulel, 2005; Izani Wan, 2008; Seyon, 2007), with the total doses varying between 2.4g and 4.8g. In 2 RCTs the N-acetylcysteine was administered intravenously (Koc, 2012; Kotlyar, 2005) with total doses varying between 0.6g and 2.4g. The follow-up time (for laboratory parameters) in the studies varied between 2 days and 30 days.

Results

CT scans, normal kidney function

Hsu (2012) reported that 8/106 patients in the NAC group versus 15/103 patients in the control group developed PC-AKI; this difference was not significant: Relative Risk (RR): 0.12 (95% CI: 0.01 to 2.11).

CT scans, impaired kidney function

Pooling of data of 5 RCTs (Kama, 2014; 2006; Kitzler, 2012; Poletti, 2007; Poletti, 2013; Tepel, 2000) with 386 patients with 60 events showed that risk ratio of PC-AKI was not reduced significantly in the NAC group: RR: 0.64 (95% CI: 0.24 to 1.70), $p=0.37$, see Figure 7.4.

Coronary angiography, normal kidney function

Pooling of data of 8 RCTs (Carbonell, 2007; Jaffrey, 2012; Kim, 2010; Kinbara, 2010; Lawlor, 2007; Sadat, 2011; Tanaka, 2011; Thiele, 2010) with 3093 patients with 394 events showed that risk ratio of PC-AKI was not reduced in the NAC group: RR: 0.97 (0.74 to 1.28); $p=0.82$, see Figure 7.5.

Coronary angiography, impaired kidney function

Pooling of data of 8 RCTs (ACT, 2011; Castini, 2010; Ferrario, 2009; Gulel, 2005; Habib, 2016; Izani Wan, 2008; Koc, 2012; Kollyar, 2005; Sadineni, 2017; Seyon, 2007) with 1388 patients with 146 events showed that risk ratio of PC-AKI was not reduced in the NAC group: RR: 0.71 (0.51 to 0.98); $p=0.16$, see Figure 7.6.

Quality of evidence

The quality of evidence for the outcome PC-AKI was downgraded by two for imprecision (low number of events and overlap with 10% border of clinical significance) for all analyses.

Figure 7.4 Meta-analysis of NAC vs. Placebo in CT with intravenous CM administration in patients with eGFR <60 ml/min/1.73m².

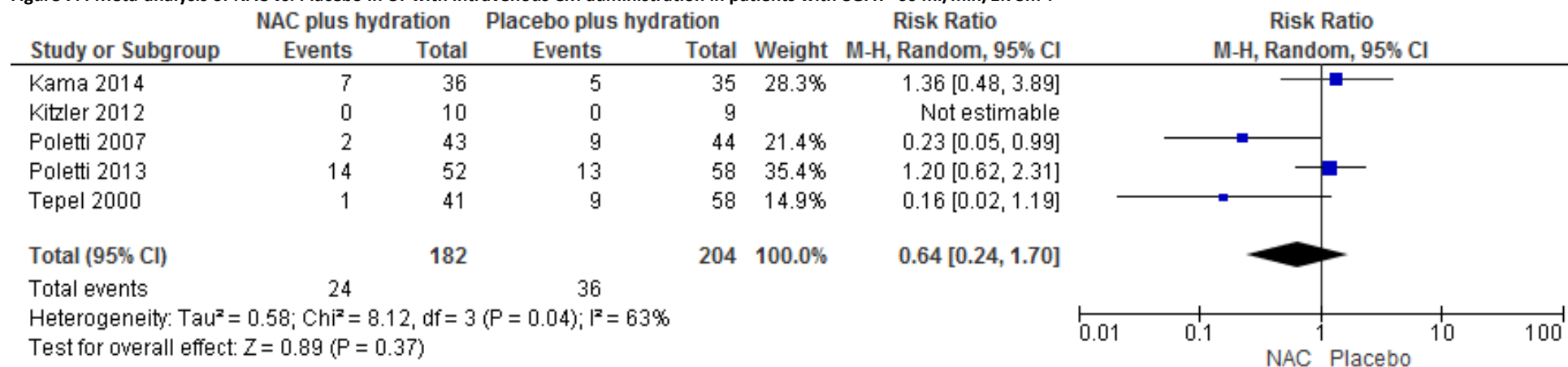


Figure 7.5 Meta-analysis of NAC vs. Placebo in Coronary angiography with intra-arterial CM administration in patients with normal kidney function

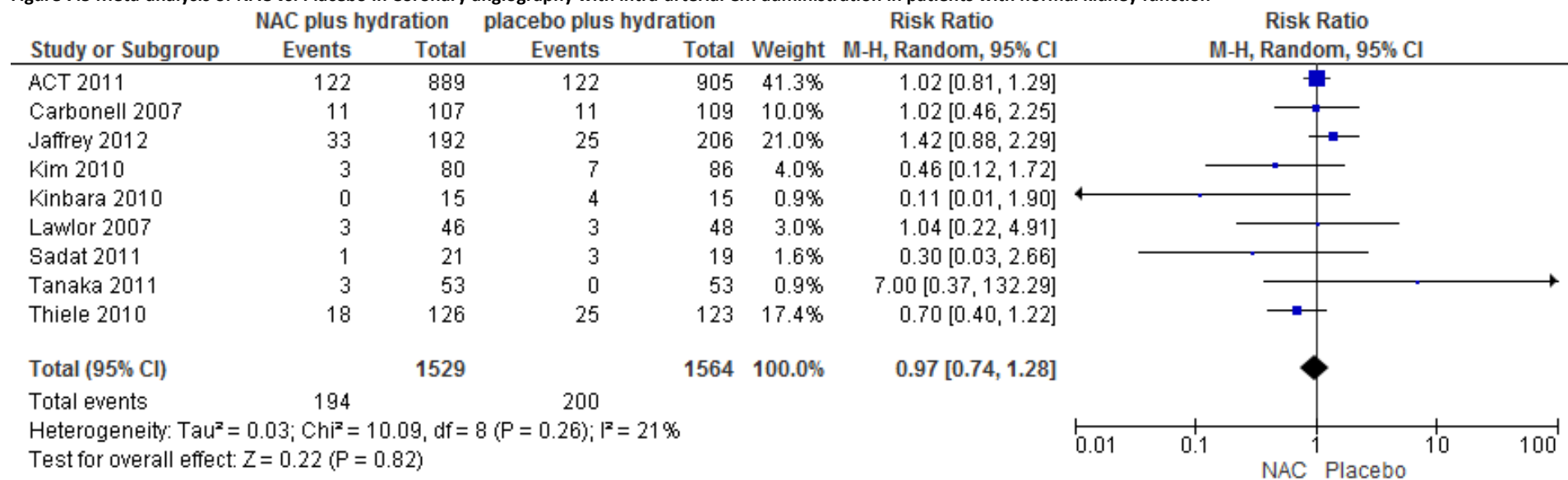
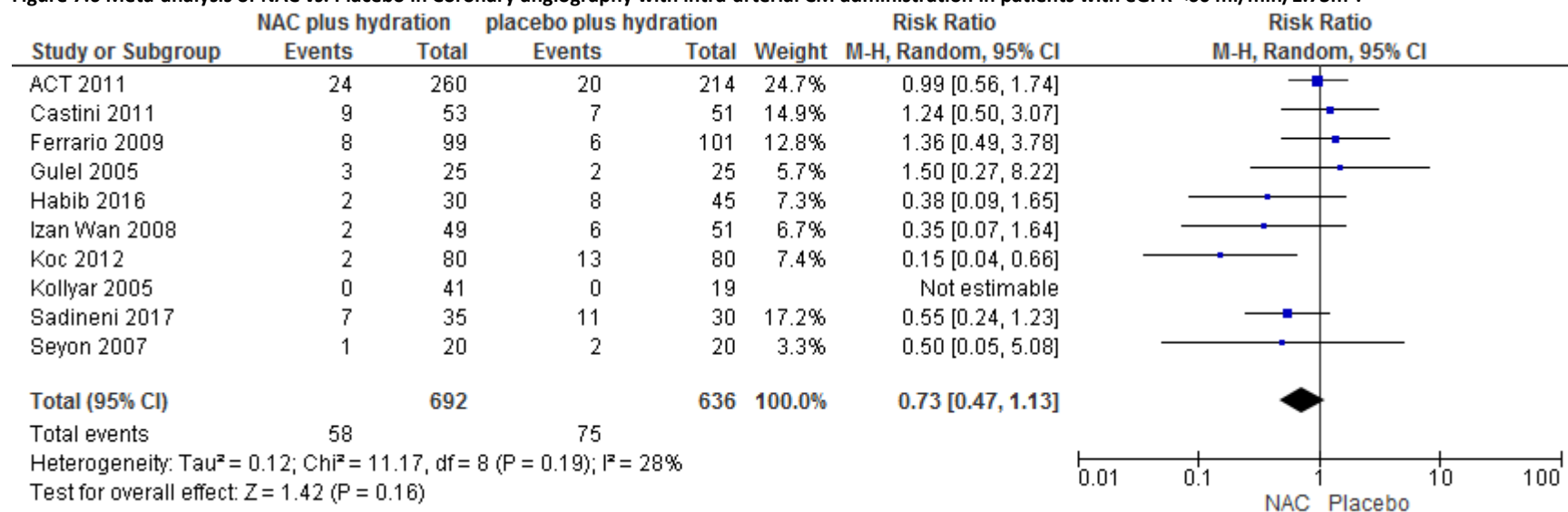


Figure 7.6 Meta-analysis of NAC vs. Placebo in Coronary angiography with intra-arterial CM administration in patients with eGFR <60 ml/min/1.73m².



Conclusions

Low GRADE	<p>There is evidence of low quality that N-acetylcysteine does not reduce the risk of PC-AKI in patients with normal kidney function undergoing computer tomography with intravascular iodine-containing contrast administration when compared to placebo.</p> <p><i>(Hsu, 2012)</i></p>
Low GRADE	<p>There is evidence of low quality that N-acetylcysteine does not reduce the risk of PC-AKI in patients with impaired kidney function undergoing computed tomography with intravascular iodine-containing contrast administration when compared to placebo.</p> <p><i>(Kama, 2014; 2006; Kitzler, 2012; Poletti, 2007; Poletti, 2013; Tepel, 2000)</i></p>
Low GRADE	<p>There is evidence of low quality that N-acetylcysteine does not reduce the risk of PC-AKI in patients with normal kidney function undergoing coronary angiography with intravascular iodine-containing contrast administration when compared to placebo.</p> <p><i>(Berwanger, 2013; Carbonell 2007; Jaffrey, 2015; Kim, 2010; Kinbara, 2010; Lawlor, 2007; Sadat, 2011; Sandhu, 2006; Tanaka, 2011; Thiele 2010)</i></p>
Low GRADE	<p>There is evidence of low quality that N-acetylcysteine does not reduce the risk of PC-AKI in patients with decreased kidney function undergoing coronary angiography with intravascular iodine-containing contrast administration when compared to placebo.</p> <p><i>(ACT, 2011; Castini, 2010; Ferrario, 2009; Gulel, 2005; Habib, 2016, Izani Wan, 2008; Koc, 2012; Kollyar, 2005; Sadenini, 2017; Seyon, 2007)</i></p>
	<p>No studies were found that compared oral to intravenous N-acetylcysteine route of administration in patients undergoing intravascular iodine-containing contrast administration.</p>

Considerations

Our meta-analysis regarding patients with a normal renal function yielded no benefit of NAC for prevention of PC-AKI, both for patients receiving CT scan and/or for patients undergoing CAG.

The evidence regarding NAC benefit for prevention of PC-AKI in patients with an impaired renal function is weak due to the quality of the trials and the heterogeneity of the results. For example, follow-up time was only 2 to 5 days in the majority of included studies; thus meaningful conclusions could not be drawn about the consequences of NAC use for mid and long term morbidity and mortality. Furthermore, the studies were not powered to draw conclusions about morbidity and mortality, only for the short-term PC-AKI laboratory diagnosis.

A meta-analysis (Sun, 2013) concluded that the evidence on use of IV NAC to prevent PC-AKI was too inconsistent to determine the efficacy. Another meta-analysis concluded that NAC may help to prevent PC-AKI in patients undergoing coronary angiography, but does not have any impact on clinical outcomes such as dialysis or mortality (Subramanian, 2016). Furthermore, the dose and route of administration of NAC differed between studies. In our own meta-analysis for patients with an impaired kidney function the use of NAC did not decrease the risk of PC-AKI significantly. Of note, only studies that described hydration strategies representative to those used in the Netherlands were included in this analysis. No studies were found that compared oral to intravenous N-acetylcysteine route of administration in patients undergoing intravascular contrast administration.

Intervention with NAC is without risk, cheap, and generally available, and there are theoretical arguments that NAC may provide reduction of CI-AKI. Despite the theoretically potential kidney protection arguments, we do not recommend adding NAC to hydration routinely in patients with an impaired kidney function. Reason is that the level of evidence is weak and the demonstrated benefit is small at best, and clinically not proven relevant. Moreover, the low cost of NAC itself is offset by extra handling time and a more complex AKI preventive protocol, which are unnecessary confounding and cost enhancing factors. None of the studies showed significant differences in clinical meaningful endpoints such as need of renal replacement therapy and/or mortality.

Recommendation

Do not use NAC for the prevention of PC-AKI in patients with a normal or impaired (eGFR <60 ml/min/1,73m²) kidney function.

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7.3 Should prophylactic Vitamin C in addition to hydration be recommended to reduce the incidence of PC-AKI in patients with pre-existent reduced kidney function receiving iodine-containing intravascular contrast medium?

Introduction

The mechanism of PC-AKI is not completely understood. However, direct cell damage by the contrast medium with subsequent oxidative stress, endothelial dysfunction and decreased nitric oxide (NO) availability are supposed to play a major role. Intrarenal NO is crucial for maintaining perfusion and oxygen supply in the renal medulla. NO depletion causes vasoconstriction with hypoperfusion of the renal medulla and local hypoxia. In addition, NO depletion affects tubular fluid composition, tubuloglomerular feed-back signaling and decreases glomerular filtration rate (Liu, 2014).

Vitamin C (ascorbic acid) is the most effective circulating antioxidant (Frei, 1990). Ascorbate specifically protects the endothelium, NO and tetrahydrobiopterin (BH4), the co-factor of NO synthase, from oxidation. Thus, vitamin C may reduce renal oxidative damage and improve the renal microcirculation. For an optimal antioxidant effect, high vitamin C plasma concentrations seem to be needed, requiring pharmacological doses (Oudemans-van Straaten, 2014).

Search question

Can prophylactic vitamin C administration in addition to hydration reduce the incidence of PC-AKI in patients with pre-existent reduced kidney function receiving intravascular contrast?

Literature search and selection

To answer our clinical question a systematic literature analysis was performed for the following research question:

Can prophylactic intravenous Vitamin C/ascorbic acid in addition to hydration reduce the incidence of CI-AKI in patients with pre-existent reduced kidney function receiving intravascular contrast?

- P (patient category) patients undergoing radiological examinations or interventions with reduced kidney function ($eGFR < 60 \text{ ml/min/1.73m}^2$) receiving intravascular iodine-containing contrast media;
- I (intervention) vitamin C/ascorbic acid/ascorbate in combination with hydration, Vitamin C alone;
- C (comparison) hydration alone, no preventive measures;
- O (outcome) Post Contrast AKI (PC-AKI), start renal replacement therapy, chronic decrease in residual kidney function.

Relevant outcome measures

The working group considered PC-AKI, mortality, start renal replacement therapy, decrease in residual kidney function, critical outcome measures and the low risk, costs and general availability of the vitamin C intervention important factors for the decision-making process.

A difference of at least 10% in relative risk was defined as a clinically relevant difference, by expert opinion of the working group (no literature was available to substantiate the decision). To illustrate, if PC-AKI occurs with an incidence of 10% in the patient population, a difference of 10% of relative risk would mean a difference of 1% in absolute risk. Thus the number needed to treat would be 100, ergo: a doctor would need to treat 100 patients to prevent one case of PC-AKI. When the incidence of PC-AKI is 5%, a difference of 10% in relative risk would mean a difference of 0.5% in absolute risk, and a number needed to treat of 200.

Search and select (method)

The data bases Medline (OVID), Embase and the Cochrane Library were searched from January 1995 to 29th of June 2015 using relevant search terms for systematic reviews (SRs) and randomized controlled trials (RCTs). This search was updated on May 3rd 2017. A total of 127 studies were found. The initial literature search procured 113 hits and a total of 14 were added after the update.

The following search criteria were applied:

- randomized controlled trial or meta-analysis;
- adult patients who underwent radiological examination or intervention using intravascular contrast media;
- patients with impaired kidney function ($eGFR < 60 \text{ ml/min/1.73m}^2$);
- hydration types: hydration with intravenous (i.v.) NaCl or bicarbonate, oral hydration;
- vitamin C that was administered in one of treatment arms i.v. or orally;
- the control arm consisted of patients that received hydration only;
- at least one of the outcome measures was described: PC-AKI, start dialysis, chronic decrease in kidney function, adverse effects of hydration (fluid overload, intensive care unit admission, mortality), cost-effectivity.

Based on title and abstract 38 studies were initially selected. After examination of full text, 35 studies were excluded, leaving 3 studies to be included in the literature summary. Reasons for exclusion are described in the exclusion table.

Results

Three studies were included in the literature analysis; one meta-analysis and two randomized controlled studies. The most important study characteristics and results are included in the evidence tables. The evidence tables and assessment of individual study quality are included in the Appendix.

Summary of literature

Description of studies

All studies were performed in patients undergoing CAG with or without PCI. The contrast medium was therefore administered via the arterial route before the kidneys in all patients.

The systematic review and meta-analysis of Sadat, 2013 included a total of 1536 patients in nine studies. We excluded four of the studies included in the Sadat meta-analysis. One of these because the control arm used N-acetylcysteine (Jo), one study because it did

not restrict inclusion to patients with chronic kidney dysfunction (Hamdi, 2013) and two studies, because they only appeared in abstract form (Li, 2012; Komiyama, 2011). All randomized controlled trials are presented in table 7.7. Vitamin C was administered orally in four studies, intravenously in two, and both orally and intravenously in two. All patients received hydration. Definition for inclusion kidney dysfunction differed between studies (sCr > 1.1 to 1.4mg/dL in 4 studies; CrCl ≤60 ml/min in 1 study;). The two studies that were only available in abstract form did not report renal dysfunction inclusion criteria.

We additionally included 2 RCTs that appeared after the Sadat meta-analysis. These trials included a total of 510 patients undergoing coronary angiography with or without intervention comparing oral vitamin C to control and using saline hydration in both arms (Dvoršak, 2013; Komiyama, 2017).

No studies were found evaluating effects of ascorbic acid administration on post-contrast acute kidney injury in patients undergoing computer tomography (CT) scans with intravascular contrast administration.

Table 7.7 Description of the studies regarding dose and route of vitamin C, type of hydration and incidence of PC-AKI

	Country Abstract	Inclusion	Dose of ascorbic acid	Route of Vit C	Normal saline iv hydration	Incidence Vit C (%)	Incidence Control (%)
Spargias 2005	Greece	SCr >106 µmol/L	3 g at least 2-h before contrast, 2 g night before and morning after	oral	50-125 ml/h iv from randomization to 6-h after	9.3	20.4
Boscheri 2007	Germany	SCr >124 µmol/L	1 g 20 min before contrast	oral	500 ml before contrast 500 ml during/after for 6-h	6.8	4.3
Zhou 2012	China	SCr >97 µmol/L	3 g iv morning of procedure 0.5 g oral night before and morning after	iv and oral	1ml/kg/h for 4-h before and at least 12-h after	7.3	5.4
Komiyama ^a 2011	Japan Abstract	Baseline renal insufficiency	3 g before procedure 2 g night and morning after	iv	1.5 – 2L	8.6	52.2
Brueck 2013	Germany	Cr clearance <60 ml/min Germany	0.5 g in 250 ml NS in 30 min 24-h and 1-h before	iv	1 ml/kg/h 12-h before and 12-h after	24.5	32.1
Li ^a 2012 (A)	China Abstract	Baseline renal insufficiency	3 g iv 2-4-h before procedure Oral 1 g on d-1 and d-2 after	iv and oral	hydration	6.4	5,6
Albabbain 2013	Saudi Arabia	SCr >112 µmol/L	3 h 2-h before, 2 g after 2 g 24-h after	oral	50-125 ml/u from randomization until 6-h after	3.3	7.3
Dvorzak 2013	Slovenia	SCr >106 µmol/L	3 g before, 2 g night before and morning after	oral	50-100 ml/h for 2-h before and 6-h after	5	7.3
Hamdi ^{a,b} 2013	Tunesia Abstract	All, Exclusion: chronic dialysis, AKI, heart failure, use of Vit C Baseline SCr 98.6 ± 29 µmol/L	3 g 2-h before, 2 g after and next day	Not reported	Not reported	11.3	21.1
Komiyama 2017	Japan	Renal dysfunction (eGFR <60 mL/min/1.73 m ²)	3g before the procedure, 2g after and the next day in combination with 20 mEq (in 20 ml) sodium bicarbonate before the procedure in the ascorbic acid group.	iv	1.5 mL/kg/h 6–15 h before and during the procedure .2.5 mL/kg/h for 6 h after the procedure in both groups. The total amount 1,500–2,500 mL	2.8	8.7

^a not included in the final meta-analysis because the study has appeared only in abstract form up to now

^b not included in the final meta-analysis because the study did not report restricting inclusion to patients with decreased kidney function

Results

Dvoršak, 2013 and Komiyama, 2017 reported that of the patients in the ascorbic acid group 2/40 (5%) and 6/211 (3%) developed PC-AKI, respectively (rise in serum creatinine >25%), compared to 3/41 (7%) and 19/218 (9%) patients in the placebo group. The difference in the study of Komiyama, 2017 was statistically significant ($p=0.008$), but not in the study of Dvoršak. None of patients required dialysis treatment.

Sadat, 2013 found 9 RCTs with a total of 1576 patients, 780 in the ascorbic acid group and 796 in the control group; and a total of 209 events, a total of 73 in the ascorbic acid group and 137 in the control group. Pooled results of Sadat, 2013 showed that ascorbic acid significantly decreased the risk of CI-AKI compared to no ascorbic acid administration: risk ratio of 0.67 (95% CI: 0.47 – 0.97, $p=0.03$, random effects model).

Meta-analyses

Three meta-analyses are reported

First, in the final meta-analysis (figure 7.8), we pooled the results of 5 RCTs from the meta-analysis of Sadat, 2013 (see above) and the studies of Dvoršak, 2013 and Komiyama, 2017. Ascorbic acid appears to significantly decrease the risk of CI-AKI: risk ratio 0.65 (95% CI: 0.453 – 0.92, $p=0.02$, random effects model) in patients undergoing coronary angiography. The meta-analysis is shown in figure 7.8.

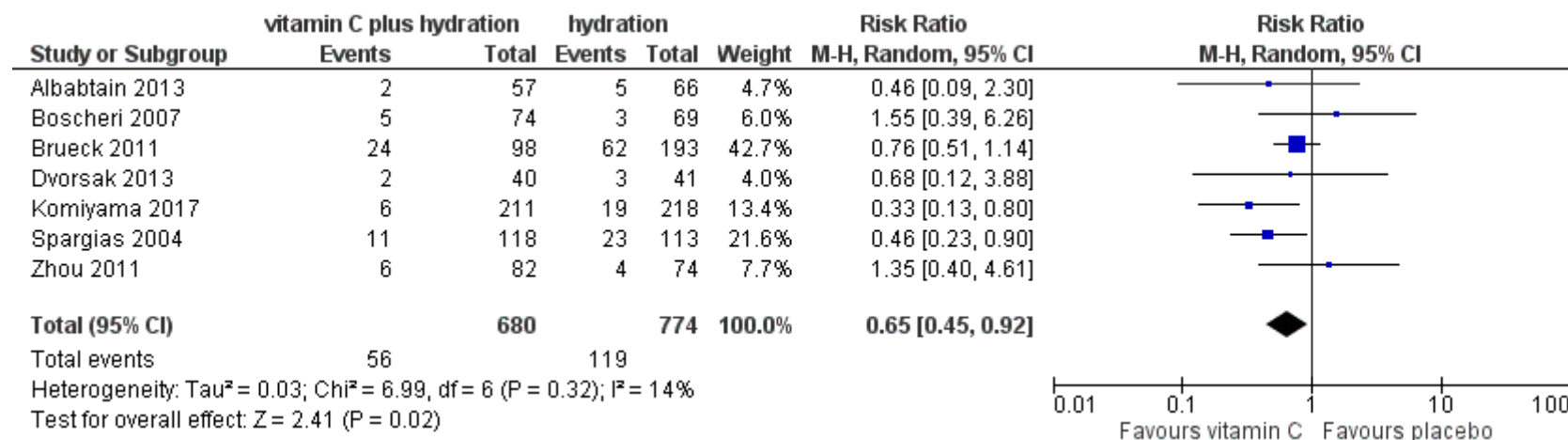
Due to high heterogeneity of the included studies and the high imprecision noted in the meta-analysis of pooled data above, no separate meta-analyses were performed for oral and intravenous vitamin C administration.

Two other meta-analyses are presented as well in the Appendix. One including the studies that appeared in abstract form as well (figure 2) and one including all RCTs on vitamin C (figure 7.10). Both demonstrate a similar effect as the meta-analysis in figure 7.8.

Quality of evidence

The level of quality of evidence was decreased from level high to level moderate, due to imprecision (total number of events <300 per group) and inconsistency (inexplicable variation in incidence of events between studies).

Figure 7.8 Meta-analysis of Vitamin C in patients undergoing coronary angiography



Conclusions

Low GRADE	There is evidence of low quality that administration of vitamin C (oral or intravenous) in addition to hydration is more effective than no administration of vitamin C for the prevention of PC-AKI in patients with eGFR<60 ml/min/1.73m ² undergoing coronary angiography. <i>(Komiyama, 2017; Dvoršak, 2013; Sadat, 2013)</i>
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	No studies were found evaluating the effects of vitamin C administration on PC-AKI in patients undergoing CT scans with intravascular contrast administration.
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Considerations

The present search shows that that vitamin C offers some protection against PC-AKI in patients with CKD undergoing coronary angiography with or without intervention. However, the risk reduction was less than of 10% and therefore not considered to be clinically relevant. Furthermore, the evidence is weak due to the quality of the trials and the heterogeneity of the results. Finally, the dose and route of administration of vitamin C differed between studies, and the incidence of PC-AKI in the control arm greatly differed among studies, ranging from 4% to 32%.

Because of this marginal protection, the Working Group does not recommend adding vitamin C to hydration routinely in patients with an increased risk of PC-AKI. Reasons are that the level of evidence is weak and the potential benefit is small and clinically likely not relevant. In addition, none of the studies showed significant differences in clinical meaningful endpoints such as need of renal replacement therapy. Since the risk of renal replacement therapy after intravascular contrast media administration is low, none of the studies was powered to show such result.

Intervention with vitamin C is without risk, cheap, and generally available, and some protection seems likely. The addition of vitamin C to hydration may therefore be considered in patients with a very high risk of PC-AKI such as those with eGFR <30 ml/min/1.73 m². Although several doses of vitamin C were used, most positive studies used a dose of 3 g orally 2 hours before the contrast, and 2 g the night before and day after the contrast administration. Since oral vitamin C is generally available and the oral route is cheapest, we suggest using this dose if the risk of AKI is considered extremely high and maximal renal protection is wanted. However, the evidence for this recommendation is very low.

Recommendation

Do not use vitamin C exclusively for the prevention of Post Contrast Acute Kidney Injury (PC-AKI) in patients with a normal or impaired (eGFR <60 ml/min/1,73m ²) kidney function.
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7.4 Should nephrotoxic medication be discontinued prior to intravascular contrast administration to reduce the risk of post contrast acute kidney injury (PC-AKI)?

Introduction

The use of non-steroidal anti-inflammatory drugs, diuretics, ACE-inhibitors or angiotensin receptor blockers has been associated with an increased risk of acute kidney injury in patients receiving intravascular iodine-containing contrast. Several international guidelines therefore advise to withhold these drugs in patients undergoing elective procedures requiring intravascular contrast administration. Implementation is however difficult, discontinuation is not without risk and whether withholding these agents in the day(s) prior to or following iodine-containing contrast administration protects patients from developing adverse renal outcomes such as acute kidney injury, long term renal injury, or a need for dialysis is an issue of debate.

The present literature search aims to answer the following questions:

1. Do withholding non-steroidal anti-inflammatory drugs, diuretics, ACE-inhibitors or angiotensin receptor blockers 24-48 hours prior to CM-enhanced CT reduce the risk of adverse renal outcomes?
2. Do withholding non-steroidal anti-inflammatory drugs, diuretics, ACE-inhibitors or angiotensin receptor blockers 24-48 hours following CM-enhanced CT reduce the risk of adverse renal outcomes?
3. Do withholding non-steroidal anti-inflammatory drugs, diuretics, ACE-inhibitors or angiotensin receptor blockers 24-48 hours prior to elective cardiovascular diagnostic or therapeutic contrast procedures reduce the risk of adverse renal outcomes?
4. Do withholding non-steroidal anti-inflammatory drugs, diuretics, ACE-inhibitors or angiotensin receptor blockers 24-48 hours following elective cardiovascular diagnostic or therapeutic contrast procedures reduce the risk of adverse renal outcomes?

Literature search and selection

To answer our clinical question a systematic literature analysis was performed for the following research questions:

1. Do withholding non-steroidal anti-inflammatory drugs, diuretics, ACE-inhibitors or angiotensin receptor blockers 24-48 hours prior to CE-CT reduce the risk of adverse renal outcomes?
2. Do withholding non-steroidal anti-inflammatory drugs, diuretics, ACE-inhibitors or angiotensin receptor blockers 24-48 hours following CE-CT reduce the risk of adverse renal outcomes?
3. Do withholding non-steroidal anti-inflammatory drugs, diuretics, ACE-inhibitors or angiotensin receptor blockers 24-48 hours prior to elective cardiovascular diagnostic or therapeutic contrast procedures reduce the risk of adverse renal outcomes?
4. Do withholding non-steroidal anti-inflammatory drugs, diuretics, ACE-inhibitors or angiotensin receptor blockers 24-48 hours following elective cardiovascular diagnostic or therapeutic contrast procedures reduce the risk of adverse renal outcomes?

P (patient category)	patients with mild to moderate chronic kidney disease undergoing radiological examinations with intravascular contrast media and using diuretics, NSAIDs, angiotensin receptor blockers, or ACE-inhibitors);
I (intervention)	cessation of non-steroidal anti-inflammatory drugs, diuretics, ACE-inhibitors or angiotensin receptor blockers prior and/or after radiological examinations with contrast media;
C (comparison)	continuation of non-steroidal anti-inflammatory drugs, diuretics, ACE-inhibitors or angiotensin receptor blockers prior and/or after radiological examinations with contrast media;
O (outcome)	post contrast acute kidney injury, start dialysis, decrease in residual kidney function, adverse events, mortality.

Relevant outcome measures

The working group considered PC-AKI, mortality, start dialysis, decrease in residual kidney function, critical outcome measures for the decision making process and adverse effects of withholding medication important outcome measures for the decision making process.

A difference of at least 10% in relative risk was defined as a clinically relevant difference; by expert opinion of the working group (no literature was available to substantiate the decision). To illustrate, if PC-AKI occurs with an incidence of 10% in the patient population, a difference of 10% of relative risk would mean a difference of 1% in absolute risk. Thus the number needed to treat would be 100, ergo: a doctor would need to treat 100 patients to prevent one case of PC-AKI. When the incidence of PC-AKI is 5%, a difference of 10% in relative risk would mean a difference of 0.5% in absolute risk, and a number needed to treat of 200.

Search and select (method)

The data bases Medline (OVID), Embase and the Cochrane Library were searched from January 2000 to 27th of August 2015 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). A search update was performed on the 3rd of May 2017. Search terms are shown. The literature search procured 379 hits. The initial search contained 320 hits, and the search update produced another 49 hits.

Studies were selected based on the following criteria:

- adult patients who underwent diagnostic or therapeutic procedures requiring intravascular administration of contrast media (CE-CT and elective cardiovascular diagnostic or therapeutic contrast procedures) and who were using diuretics, NSAIDs, angiotensin receptor blockers, or ACE-inhibitors;
- patients with impaired kidney function, at least eGFR <60 ml/min/1,73m² or serum creatinine ≥ 132 µmol/l;
- the use of NSAIDs, diuretics, ACE-inhibitors, or angiotensin receptor blockers was stopped at least 24 hours prior to radiological examination using contrast media OR nephrotoxic medication was discontinued at least 24 hours following radiological examination using contrast media;
- at least one of the outcome measures was described: PC-AKI, start dialysis, decrease in residual kidney function, mortality.

Based on title and abstract a total of 39 studies were selected, all from the initial search. After examination of full text a total of 37 studies were excluded and 2 studies definitely included in the literature summary.

Two studies were included in the final literature analysis, the most important study characteristics and results were included in the evidence tables. The evidence tables and assessment of individual study quality are included.

Summary of literature:

ACE inhibitors and Angiotensin-II Receptor Blockers

Description of studies

This literature summary describes 2 randomized controlled trials (RCTs) (Bailey, 2015; Rosenstock, 2008).

Rosenstock, 2008 compared discontinuation of angiotensin converting enzyme (ACE)-inhibitors to continuation of ACE-inhibitors prior to coronary angiography in terms of kidney damage. A total of 283 patients were enrolled in this study of which 220 patients were randomized: 113 chronic (>2 months) ACE-inhibitor users who continued their therapy; 107 chronic ACE-inhibitor users who discontinued ACE-inhibitors (withheld the morning of procedure to 24 hours after procedure). A third group of 68 patients who were not using ACE-inhibitors was also followed. All patients had chronic kidney disease (eGFR 15-60ml/min/1.73m²). Patients were hydrated based on the institution's policies and medication such as metformin and diuretics were held prior to the procedure in all patients. Creatinine values were measured at baseline and 24 hours post-procedure; further measurements were at the discretion of the treating physician.

Bailey, 2015 compared discontinuation of Angiotensin II blockade medication (combination of ACE inhibitors and angiotensin receptor blockers (ARB)) versus continuation of Angiotensin II blockade medication prior to cardiac catheterization in terms of kidney damage.

Bailey, 2015 included 208 patients with moderate renal insufficiency ($\geq 150 \mu\text{mol/l}$ within three months or $\geq 132 \mu\text{mol/l}$ within one week of cardiac catheterisation). Use of angiotensin II blockers was stopped in 106 patients and continued in 102 patients. In the discontinuation group, Angiotensin II medication was stopped at least 24 hours prior to catheterisation and restarted 96 hours post procedurally. Both groups received 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. Serum creatinine levels were obtained 72 \pm 24 hours post procedurally.

No literature was found describing discontinuation of NSAIDs or diuretics prior to CM-enhanced CT in patients with impaired kidney function.

Results

Rosen stock, 2008

The incidence of PC-AKI in the 113 ACE-inhibitor users in whom medication was continued was 6.2% (95% CI: 2.5 to 12%). The incidence of PC-AKI was 3.7% (95% CI: 1 to

9%) in the discontinuation group (n=107) and 6.3% in the ACE-inhibitor naïve group (n=68). The differences in incidences were not significant (p=0.66).

Baines, 2015

PC-AKI occurred in 18.4% of the patients who continued Angiotensin II blockers and in 10.9% of the patients in whom Angiotensin II receptor blockers were discontinued (hazard ratio (HR) of discontinuation group: 0.59, 95% CI: 0.30 to 1.19; p=0.16). The change in mean serum creatinine was 27 (SD 44) µmol/L in the group that continued Angiotensin II blockers and 9 (SD 27) µmol/L, in the patients who discontinued the drug, p=0.03. There was 1 death (1%), 1 ischemic stroke (1%) and 3 patients were hospitalized for cardiovascular cause (3%) in the group where ACE-inhibitors were continued; versus no clinical events in the discontinuation group (p=0.03, study size not powered for this analysis).

Quality of evidence

For Rosenstock, 2008 the quality of evidence was downgraded by 2 levels due to indirectness (only kidney function after 24 hours available).

For Baine, 2015 the quality of evidence was downgraded by 2 levels due to imprecision and limitations in study design and further downgraded for the outcomes mortality, dialysis and cardiovascular events for 1 more level for imprecision (study underpowered to draw conclusions about this outcome).

Due to heterogeneity in types of medications and interventions for which contrast administration was used, it was not possible to pool the study results.

Conclusions

Low GRADE	<p>There is a low level of evidence that discontinuation of ACE-inhibitors (on day of procedure up to 24 hours after procedure) does not reduce the risk of post contrast acute kidney injury compared to continuing ACE-inhibitor use around angiography in patients with chronic kidney disease.</p> <p><i>(Rosenstock, 2008)</i></p>
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Low GRADE	<p>There is a low level of evidence that discontinuation of Angiotensin-II receptor blockers (24 hours before procedure up to 96 hours after procedure) does not reduce the risk of post contrast acute kidney injury compared with continuing Angiotensin II receptor blocker use around cardiac catheterization in patients with moderate kidney insufficiency.</p> <p><i>(Baine, 2015)</i></p>
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Very Low GRADE	<p>There is a very low level of evidence that continuation of Angiotensin II receptor blockers (24 hours before procedure up to 96 hours after procedure) could be associated with more adverse events compared to discontinuation of Angiotensin II blocker use around cardiac catheterization in patients with moderate kidney insufficiency.</p> <p><i>(Bainey, 2015)</i></p>
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	<p>There is no evidence that discontinuation of NSAIDs or diuretics before the administration of intravascular contrast in euvolemic patients reduces the risk of post contrast acute kidney injury (PC-AKI) compared with continuation of diuretics.</p>
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Considerations

The use of non-steroidal anti-inflammatory drugs, diuretics, ACE-inhibitors or angiotensin II receptor blockers has been associated with an increased risk of acute kidney injury following intravascular iodine-containing contrast administration. This has led to the perception that withholding these agents is a useful strategy to prevent acute kidney injury. However, there is insufficient scientific evidence to support this hypothesis.

ACE-inhibitors and Angiotensin II Receptor Blockers.

First of all, the only two randomized controlled trials regarding this research question address discontinuation of ACE-inhibitors or angiotensin II receptor blockers.

Second, the two RCTs that have been performed included a small number of patients and restricted their inclusion to patients undergoing coronary angiography/catheterization. Hence, no information is available on the effect of withholding or continuing ACE-inhibitors or angiotensin receptor blockers in chronic kidney disease patients undergoing intravenous contrast enhanced-CT.

An important aspect that should be taken into consideration is the fact that observational studies showing an association between the risk of PC-AKI and the use of diuretics, ACE-inhibitors or angiotensin receptor blockers might have been confounded by the indication for the use of these drugs. Patients with congestive heart failure, for instance, are at increased risk of developing PC-AKI and are likely to use ACE-inhibitors.

Finally, and most importantly, ACE-inhibitors and angiotensin receptor blockers are not nephrotoxic, although they are referred to as nephrotoxic drugs by guidelines and in literature. ACE-inhibitors and angiotensin receptor blockers inhibit angiotensin-induced post-glomerular vasoconstriction. As a result, these drugs may improve medullary perfusion and may therefore be nephroprotective under certain conditions. However, postglomerular vasoconstriction increases filtration pressure. Thus, if glomerular filtration depends on postglomerular filtration, which may be the case in patients with renal artery stenosis, hypovolemia or very poor cardiac output, the use ACE-inhibitors and angiotensin receptor blockers can reduce glomerular filtration, a fully reversible process. Thus, patients with very low glomerular reserve capacity which are dependent of postglomerular vasoconstriction may benefit from a temporary discontinuation of

ACE-inhibitors and angiotensin receptor blockers regarding maintenance of glomerular filtration. Anyway, hypovolemia should always be corrected before administering iodine-containing CM. The working group therefore considers nephrology consultation before administering iodine-containing CM in patients with $eGFR < 30 \text{ ml/kg/1.73m}^2$ crucial to individualize continuation or discontinuation of ACE-inhibitors and Angiotensin Receptor Blockers.

NSAIDs

To our knowledge, no RCTs have been performed on cessation of diuretics or non-steroidal anti-inflammatory drugs. Thus, an evidence based recommendation cannot be given. However, non-steroidal anti-inflammatory drugs have proven to be nephrotoxic, because they inhibit compensatory postglomerular vasodilation, on which medullary perfusion is dependent in conditions with diminished glomerular flow such as heart failure. Despite the lack of evidence, it may be considered to discontinue non-steroidal anti-inflammatory drugs in patients with chronic kidney disease undergoing contrast administration. The working group therefore considers nephrology consultation before administering iodine-containing CM in patients with $eGFR < 30 \text{ ml/kg/1.73m}^2$ crucial to individualize continuation or discontinuation of NSAIDs.

Diuretics

No RCTs were found comparing the discontinuation of diuretics to continuation of diuretics as sole intervention in the setting of intravascular contrast. However, several RCTs have been published comparing the use of diuretics in combination with different types of controlled hydration to hydration alone in patients receiving intra-arterial contrast for CAG and or PCI. These studies are reported in the chapter on optimal hydration strategy. In most of the studies, the combination of diuretics and controlled hydration was superior in preventing the risk of PC-AKI indirectly supporting the concept that the use of diuretics before using intravascular contrast does not increase the risk of PC-AKI if adequate hydration is performed.

Of note, diuretics are not nephrotoxic per se. However, the use of diuretics may hamper glomerular filtration if their use causes hypovolemia and glomerular reserves are diminished. In these cases, the additional use of iodine-containing CM may reduce glomerular filtration. Finally, withholding diuretics might increase the risk of acute heart failure in chronic users of these agents, especially in the setting of preventive hydration that is given to patients with chronic kidney disease undergoing intravascular contrast administration. The working group therefore considers nephrology consultation before administering iodine-containing CM in patients with $eGFR < 30 \text{ ml/kg/1.73m}^2$ crucial to individualize continuation or discontinuation of diuretics.

Other nephrotoxic drugs

No RCT's have been published on the effect of discontinuation of PC-AKI on the reduction of PC-AKI. Thus, there is no evidence whether discontinuation of nephrotoxic drugs will reduce the incidence of PC-AKI. Their combined use with iodine-containing CM could however increase the risk of harm to the kidney. The working group therefore recommends to consider other imaging techniques that avoid the use of iodine-containing CM and recommends nephrology consultation before administering iodine-containing CM in patients with $eGFR < 30 \text{ ml/kg/1.73m}^2$ to individualize continuation or

discontinuation of nephrotoxic drugs and weigh this against the potential benefits and harm of the administration of iodine-containing CM.

In summary, the lack of evidence of a protective effect of withholding diuretics, ACE-inhibitors or angiotensin receptor blockers, combined with the fact that withholding diuretics or ACE-inhibitors might be associated with an increased risk of acute heart failure, has resulted in the recommendation not to withhold these drugs in chronic kidney disease patients receiving intravascular contrast agents. However, the working group considers nephrology consultation before administering iodine-containing CM in patients with eGFR <30 ml/kg/1.73m² crucial to individualize continuation or discontinuation of these specific medications.

Recommendations

Do not routinely withhold ACE-inhibitors, angiotensin II receptor blockers or diuretics prior to intravascular iodine-containing contrast administration. iodine-containing

Withhold NSAIDs prior to intravascular iodine-containing contrast medium administration

The working group recommends nephrology consultation before administering iodine-containing contrast in patients with eGFR <30 ml/kg/1.73m² to individualize continuation or discontinuation of ACE inhibitors, angiotensin II receptor blockers, diuretics or nephrotoxic drugs and weigh this against the potential benefits and harm of the administration of iodine-containing CM

References

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7.5 Should prophylactic renal replacement therapy be recommended to reduce the risk of PC-AKI in patients with CKD stage 4 to 5 receiving intravascular contrast medium?

Introduction

PC-AKI may increase cardiovascular morbidity and mortality. However, it should be noted, that the incidence of PC-AKI is low and PC-AKI only occurs in the presence of patient-, disease- or contrast-related risk factors and not in a young and healthy patient.

An impaired glomerular filtration rate, especially below $30 \text{ ml/min/1.73m}^2$, seems the most important risk factor of PC-AKI. Adequate hydration during contrast administration seems the best preventive measure and bicarbonate hydration is recommended in this population (see Chapter 6).

Hemofiltration

The commonly used contrast media (CM) have a molecular weight below 1000 Da and are easily removed by hemofiltration. The sieving coefficient of iohexol is approximately 1 at ultrafiltrate rates between 1 and 6 L/h (Yardman, 2015) in vitro. However, during haemodialysis, sieving coefficient was about 1 at 1 L/h but decreased to 0.57 at 6 L/h. Thus hemofiltration reduced CM more effectively than haemodialysis.

In patients with an $\text{eGFR} < 30 \text{ ml/min/1.73m}^2$ (CKD stage 4 to 5), undergoing coronary angiography, the sieving coefficient of iopamidol during continuous hemofiltration was about 0.85 (Guastoni, 2014). A 6-hour session of continuous hemofiltration removed a similar amount of CM as did the kidneys in 12-hours (see figure 7.11). Thus in patients with CKD stage 4-5, hemofiltration significantly adds to the removal of the CM.

Figure 7.11 from Gastoni (1)

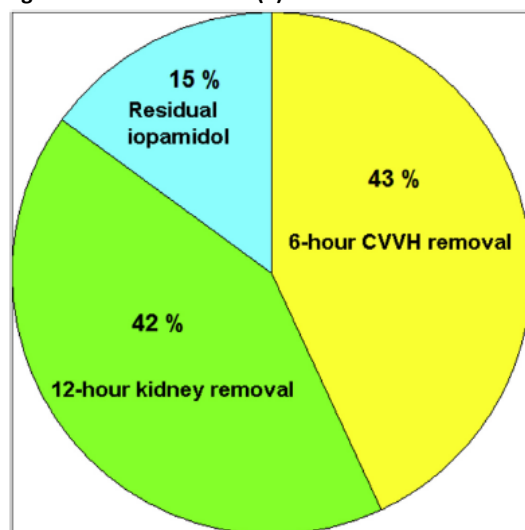


Figure 2. Iopamidol removal (expressed as percentage of total infused dose) by 6-hour CVVH and 12-hour diuresis. Residual iopamidol represents the difference between total infused iopamidol and total iopamidol removed by both kidney and CVVH.

The main aim of the present chapter is to evaluate whether *prophylactic* renal replacement therapy (RRT) reduces the incidence of PC-AKI and associated complications in patients with CKD stage 4-5 ($\text{eGFR} < 30 \text{ ml/min/1.73m}^2$) receiving intravascular iodine-containing CM.

Literature search and selection

To answer our clinical question a systematic literature analysis was performed for the following research question:

Can prophylactic hemofiltration reduce the risk of PC-AKI in patients with pre-existent reduced kidney function (pre-existent eGFR less than 30 ml/min/1.73m²) receiving intravascular contrast?

- P (patient category) patients with impaired kidney function (eGFR less than 30 ml/min/1.73m²) undergoing radiological examinations or interventions with reduced kidney function receiving intravascular contrast;
- I (intervention) hemofiltration with or without hydration;
- C (comparison) hydration alone;
- O (outcome) contrast-induced nephropathy (CIN) / contrast-associated acute kidney injury (CA-AKI), Post Contrast AKI (PC-AKI), start dialysis, chronic decrease in residual kidney function.

Relevant outcome measures

The working group considered PC-AKI, mortality, start dialysis, decrease in residual kidney function, critical outcome measures for the decision making process.,

A difference of at least 10% in relative risk was defined as a clinically relevant difference; by expert opinion of the working group (no literature was available to substantiate the decision). To illustrate, if PC-AKI occurs with an incidence of 10% in the patient population, a difference of 10% of relative risk would mean a difference of 1% in absolute risk. Thus the number needed to treat would be 100, ergo: a doctor would need to treat 100 patients to prevent one case of PC-AKI. When the incidence of PC-AKI is 5%, a difference of 10% in relative risk would mean a difference of 0.5% in absolute risk, and a number needed to treat of 200.

Search and select (method)

The data bases Medline (OVID), Embase and the Cochrane Library were searched from January 1995 to 15th of October 2015 using relevant search terms for systematic reviews (SRs) and randomized controlled trials (RCTs). A search update was performed on the 3rd of May 2017. The literature search procured 126 hits. A total of 113 papers were found in the initial search, and 14 in the search update.

The following search criteria were applied:

- randomized controlled trial or meta-analysis;
- adult patients who underwent radiological examination or intervention using intravascular contrast media;
- patients with impaired kidney function (eGFR <30 ml/min/1.73m²);
- hydration types: hydration with intravenous (i.v.) NaCl 0.9% or bicarbonate 1.4%, oral hydration;
- treatment arm consisted out of patients receiving renal replacement therapy (haemodialysis, hemodiafiltration, hemofiltration);
- the control arm consisted of patients that received hydration only;
- at least one of the outcome measures was described: Contrast-induced nephropathy (CIN) / contrast-induced acute kidney injury (CI-AKI)/PC-AKI, start

dialysis, chronic decrease in kidney function, adverse effects of hydration (fluid overload, intensive care unit admission, mortality), cost-effectiveness.

Based on title and abstract 29 studies were selected, all from the initial search. After examination of full text, 27 studies were excluded, leaving 2 studies to be included in the literature summary. Reasons for exclusion are described in the exclusion table.

Results

Two studies were included in the literature analysis, one meta-analysis and one non-randomized controlled study. The most important study characteristics and results are included in the evidence tables. The evidence tables and assessment of individual study quality are included.

Summary of literature

Description of studies

A systematic review (Cruz, 2012) and a non-randomized controlled trial (Spini, 2013) were included in this literature analysis.

Cruz (2012) studied whether periprocedural renal replacement therapy (RRT) decreased the risk of PC-AKI in patients receiving intravascular contrast media when compared to standard medical therapy (SMT). The search was preformed up to March 2011. A total of 9 randomized controlled trials (RCTs) with 751 patients and 2 observational studies with 259 patients (Hsieh, 2005; Gabutti, 2003) were included in this review. Furthermore, 7 of the included RCTs contained patients with chronic kidney disease (CKD) stage 4 and 5 (n=455) (Berger, Gabutti, Hsieh, Marenzi 2003, Marenzi 2006, Sterner, Vogt); these were pooled separately in a subanalysis. This subgroup is of specific interest regarding our question.

Spini (2013) studied 46 patients with CKD, defined as serum Creatinine >177 µmol/L or eGFR less than 30 ml/min, submitted to Percutaneous coronary intervention (PCI), who received either continuous renal replacement therapy only after PCI (CRRTpost, n=21) or CRRT before and after PCI (CRRTpre-post, n=25) in addition to saline hydration in both groups.

CRRT consisted of continuous veno-venous hemofiltration (CVVH) for patients with serum creatinine <265 µmol/L or continuous veno-venous hemodiafiltration (CVVHDF) for patients with serum creatinine >265 µmol/L, initiated 6 to 8 hours before PCI and restarted immediately post PCI for 18-24 hours (CRRTpre-post) or CRRT applied only after PCI (CRRTpost).

Of note, the study was not randomized. Whether patients received either CRRTpost or CRRTpre-post depended on logistics and preference of the attendant physician. Furthermore, the study did not include a control group receiving hydration only. Finally, the type of replacement fluid was not specified.

The main characteristics of the individual studies included in the meta-analysis and the Spini study are presented in Table 7.12.

Table 7.12 Description of the studies regarding renal replacement therapy, type of hydration and incidence of PC-AKI

Author year	Design	Inclusion	Intervention	Hydration	PC AKI RR	Risk of acute RRT	Mortality Hospital/long-term	
Hemofiltration (HF) or Hemodiafiltration (HDF)								
Gabutti 2003	Obs 49	CKD st 4	HDF during-post vs. SMT	16/26 of the RRT SMT: all	1.56 (0.66-3.72)	2.89 (0.12-67.75)	NR	NR
Marenzi 2006	RCT 92	CKD st 4-5	HF pre-post vs. HF-HDF post vs. SMT	Pre-post group: No Post group: yes SMT: yes	0.48 (0.27-0.88)	0.16 (0.05-0.55)	0% 10% 20%	NR NR
Marenzi 2003	RCT 114	CKD st 4	HF pre-post vs. SMT	HF group: No	0.12 (0.05-0.32)	0.14 (0.03-0.58)	3% 10%	14% 30%
Spini 2013	Non-RCT 46	CKD st 4-5	HF-HDF pre-post vs. HF-HDF post	Both groups	0.0499 (0.003-0.801)	8% vs. 19%	NR NR	16% 57%
Haemodialysis								
Berger 2001	RCT 15	CKD st 4	HD post vs. SMT	Both groups	3.43 (0.45-25.93)			
Frank 2003	RCT 17	CKD st 4	HD during-post vs. SMT	Both groups	Creat clearance not different			
Hsieh 2004	Obs 40	CKD st 4-5	HD post vs. SMT	70% of the RRT SMT: all	0.33 (0.01-7.72)			
Lee 2007	RCT 82	CKD st 5	HD vs. SMT	Both groups		0.07 (0.01-0.49)		
Lehnert 1998	RCT 30	CKD st 3-4	HD post vs. SMT	Both groups	1.33 (0.61-2.91)			
Sterner 2000	RCT 32	CKD st 4-5	HD post vs. SMT	Both groups	1.70 (0.59-4.90)			
Reinecke 2007	RCT 424	CKD st 3	HD post vs. SMT	Both groups	2.81 (1.43-5.52)	2.05 (0.29-14.41)		
Vogt 2001	RCT 113	CKD st 4	HD post vs. SMT	Both groups	1.27 (0.80-2.01)	2.81 (0.79-10.06)		

PC-AKI: post contrast acute kidney injury; RRT: renal replacement therapy; SMT: standard medical therapy; RCT: randomized controlled trial; CKD: chronic kidney disease, stage (st) 3 eGFR 30 to 60 ml/min/1.73m², stage 4 15-30 ml/min/1.73m², stage 5 <15 ml/min/1.73m²; HF: hemofiltration; pre-post: before and after contrast administration; post: after contrast administration; HDF: hemodiafiltration, HD: haemodialysis.

Results

Post contrast-AKI

Cruz (2012) reported that in 9 RCTs and 2 observational studies; a total of 1010 patients (n=751 for the RCTs) were included (see table 7.12). All studies included patients who underwent coronary angiography (CAG), with or without Percutaneous coronary intervention (PCI).

Studies were highly heterogeneous in type of RRT, timing of RRT, type of contrast given and type of hydration given as SMT (see Table 7.12).

Eight of the studies used haemodialysis (HD) as mode of RRT (Berger, 2001; Frank, 2003; Hsieh, 2006; Lee, 2007; Lehnert, 1998; Reinecke, 2007; Sterner, 2000; Vogt, 2001). One of these had an observational design (Hsieh, 2006) and two included patients with CKD stage 3 (Lehnert, 1998; Reinecke, 2007). These three studies were therefore not included in the analysis. Out of the five RCTs comparing HD to standard medical treatment (SMT), two only reported creatinine change after contrast medium administration (Frank, 2003; Lee, 2007) and not PC-AKI risk, and thus these studies also were excluded from the analysis. When the three RCTs comparing HD to SMT were pooled (Berger, 2001; Sterner, 2000; Vogt, 2001), the incidence of PC-AKI was 43% in the HD group and 30% in the SMT group. There was no significant difference in risk op PC-AKI in the patients receiving HD versus those who received SMT: risk ratio (RR): 1.38 (95% CI: 0.91 to 2.10; p=0.13) as shown in Figure 7.13.

Four of the included studies applied hemofiltration (HF) or hemodiafiltration (HDF). One of these compared HF before and after iodine-containing contrast (HFpre-post) to SMT (Marenzi, 2003), one study compared three groups: HFpre-post and HF after iodine-containing contrast only (HFpost) to SMT (Marenzi, 2006), one study compared HDF started just before iodine-containing contrast administration to SMT (Gabutti, 2003), and one study compared HF-HDF pre-post to HF-HDF post. The latter two studies had an observational design and were, therefore, not included in the main analysis. When the two RCTs comparing HDF to SMT were pooled (Marenzi, 2003; Marenzi, 2006) the incidence of PC-AKI was 15% in the HDF group and 53% in the SMT group. There was no significant difference in risk op PC-AKI in the patients receiving HDF versus those who received SMT: risk ratio (RR): 0.25 (95% CI: 0.06 – 1.11; p=0.07) as shown in Figure 7.14.

Figure 7.13 Pooled analysis of PC-AKI risk in CKD 4-5 patient undergoing CAG and/or PCI and receiving either HD or SMT

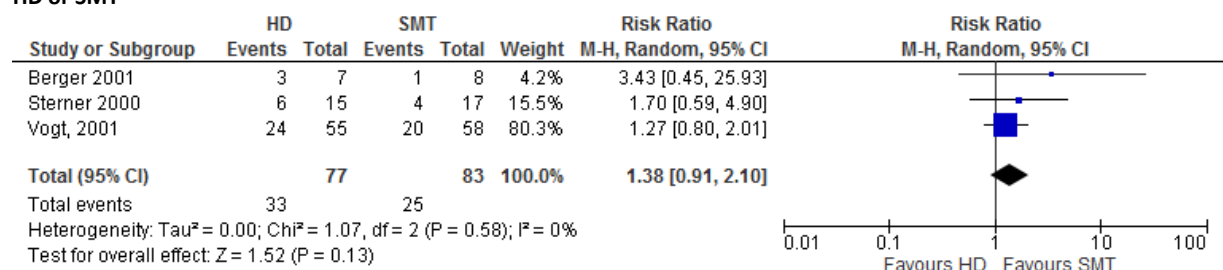
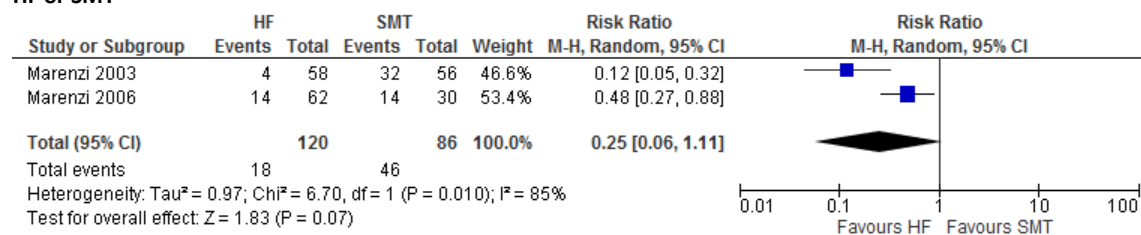


Figure 7.14 Pooled analysis of PC-AKI risk in CKD 4-5 patient undergoing CAG and/or PCI and receiving either HF or SMT



Most importantly, haemodialysis was associated with an increased risk of PC-AKI 1.38 (95% CI: 0.91 to 2.10; p=0.13), albeit this result was not statistically significant. Meanwhile HF/HDF did not reduce the occurrence of PC-AKI, but appeared to reduce the risk of acute temporary RRT (RR 0.22, 0.06-0.74). Of note, 80% of the patients receiving HF came from one centre (Cruz, 2012).

Pre- contrast medium HDF versus pre- and post-contrast medium HDF

Spini (2013) reported that none of the patients in the HF-HDFpre-post group 0/25 developed PC-AKI, while 13/21 (62%) patient in the HF-HDFpost group developed PC-AKI (RR 0.0499 (95% CI 0.003 to 0.801, p <0.001)). Furthermore, during a follow-up of 15 months (median) a worsening of kidney function was observed in 3/25 patients in the HF-HDFpre-post group compared to 9/21 in the HF-HDFpost group (p=0.042). However, this study was not randomized and might be confounded.

Three of the studies investigating pre- and post-contrast hemofiltration found a reduction of in-hospital complications (Marenzi, 2003; Marenzi, 2006; Spini, 2015).

In addition, three of the studies investigating pre- and post-contrast hemofiltration found a reduction in mortality. Marenzi (2003) and Marenzi (2006) reported a reduction in hospital mortality, while Marenzi (2003) and Spini reported a reduction in late mortality.

Quality of evidence

The quality of evidence for the outcome PC-AKI in the comparison HD or HDF versus SMT in patients with CKD 4-5 was downgraded by three points, from high to very low; one point due to heterogeneity of the included studies and two points due to wide confidence intervals of effect size (imprecision).

The quality of evidence for the outcome PC-AKI in the comparison post-CRRT versus pre- and post-CRRT was downgraded by three points, from high to very low, due to wide confidence intervals of effect size (imprecision).

Conclusions

Very Low GRADE	<p>There is a very low level of evidence that prophylactic haemodialysis does not reduce the risk of PC-AKI compared to standard medical treatment in patients with chronic kidney disease stage 4-5 (eGFR <30 ml/min/1.73m²) receiving intravascular iodine-containing contrast administration for coronary angiography with or without percutaneous intervention.</p> <p><i>(Cruz, 2012)</i></p>
Very Low GRADE	<p>There is a very low level of evidence that prophylactic hemo(dia)filtration does not reduce the risk of PC-AKI compared to standard medical treatment in patients with Chronic Kidney Disease stage 4-5 receiving intravascular iodine-containing contrast administration for coronary angiography with or without percutaneous intervention.</p> <p><i>(Cruz, 2012)</i></p>
Very Low GRADE	<p>There is a very low level of evidence that prophylactic hemo(dia)filtration reduces the risk of acute renal replacement therapy compared to standard medical treatment in patients with Chronic Kidney disease stage 4 or 5 receiving intravascular iodine-containing contrast administration for coronary angiography with or without percutaneous intervention.</p> <p><i>(Cruz, 2012)</i></p>
Very Low GRADE	<p>There is a very low level of evidence that a combination of hemodiafiltration before and after contrast administration is more effective for the prevention of PC-AKI when compared to hemodiafiltration after iodine-containing contrast administration alone, in patients undergoing percutaneous intervention.</p> <p><i>(Spini, 2013; Marenzi 2006)</i></p>

Considerations

Renal replacement therapy for the prevention of PC-AKI

The present systematic review and meta-analysis shows that prophylactic HD increases the risk of PC-AKI in patient with CKD stage 4 to 5 (eGFR <30 ml/min/1.73m²), (albeit not significantly) but also that prophylactic HF may reduce the risk of PC-AKI, the need of acute RRT and possible long term outcome, especially if applied before and after iodine-containing contrast medium administration.

A limitation of using PC-AKI as an endpoint is that creatinine, which forms the base of the PC-AKI definition, is removed by RRT. However, creatinine is removed both by HD and HF. Nevertheless, haemodialysis increases the risk of PC-AKI while HF does not. HF might even be beneficial.

A possible explanation for the harmful effect of prophylactic HD is that the risk of RRT-induced hypotension is greater when using HD compared to HF/HDF. The risk of

hypotension may especially be increased in the patients with diminished myocardial function. Continuous hemofiltration further allows for guided fluid removal and thereby prevents hydration-associated pulmonary oedema, for which patients with combined cardiac and renal dysfunction are at risk.

However, the beneficial effects of pre- and post-hemofiltration with regard to lowering the risk of PC-AKI, are only reported by one centre, if the analysis is restricted to RCTs. This limits the generalizability of the results. For this reason, we do not recommend using prophylactic hemofiltration as standard intervention in patients undergoing percutaneous coronary interventions. Pre- and post-contrast hemofiltration could however be considered in a dedicated population with combined severe renal and cardiac dysfunction having a high risk of pulmonary oedema during hydration and after intracoronary contrast administration.

Schedule of chronic dialysis

There is no literature available that answers the question whether the timing of the dialysis in regard to the timing of the contrast administration has any effect on the PC-AKI risk. It is the opinion of the working group that the scheduling of an iodine-containing contrast-enhanced imaging study does not need to be adapted to the dialysis schedule of the patient. Or vice versa: the schedule of chronic dialysis does not need to be adapted for the purpose of an iodine-containing contrast-enhanced imaging study.

Recommendation

Do not use prophylactic dialysis in patients with chronic kidney disease stage 4 to 5 receiving intravascular iodine-containing contrast medium for coronary angiography with or without percutaneous intervention, to lower the risk of post contrast acute kidney injury.

Do not use prophylactic hemofiltration routinely in patients with chronic kidney disease stage 4 to 5 receiving intravascular iodine-containing contrast medium for coronary angiography with or without percutaneous intervention.

Do not change the schedule of chronic dialysis for the purpose of an iodine-containing contrast-enhanced imaging study (or in other words: the scheduling of an iodine-containing contrast-enhanced imaging study does not need to be adapted to the dialysis schedule of the patient).

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Chapter 8 Iodine-containing CM use in type-2 diabetic patients using metformin

Clinical Question

Should metformin be discontinued in patients undergoing intravascular contrast administration for radiological examination to prevent metformin-associated lactic acidosis (MALA)?

Introduction

Metformin-associated lactic acidosis (MALA) is a rare but severe complication. Metformin is cleared by the kidney. Therefore, increased circulating and tissue metformin levels may occur when kidney function is impaired. Of note, metformin itself is not nephrotoxic. Administration of iodine-containing contrast medium (CM) can temporarily impair kidney function, thereby increasing metformin levels and the risk of MALA. In addition, the risk of kidney function impairment in response to iodine-containing CM administration may be greater in patients with diabetes. Providing kidney function is normal or moderately impaired the risk of kidney function deterioration upon CM administration is extremely low, although the risk may vary between intravenous or intra-arterial routes of contrast administration.

This raises several questions:

- Is there evidence that below a certain level of kidney function, metformin should be discontinued before CM is administered?
- Should a distinction be made between the routes of administration of CM, i.e. intravenously or intra-arterially?
- If metformin before CM administration is discontinued, when can it be restarted?

Search and selection of literature

To answer our clinical question a systematic literature analysis was performed for the following research question:

Does discontinuation of metformin or reduction of metformin-dose in diabetic patients who are subjected to i.v. or i.a. contrast administration result in a lower risk of developing lactate acidosis and/or increase the risk of a serious hyperglycaemia?

P (patient category)	diabetic patients on metformin with normal renal function or impaired renal function who are subjected to i.v. or i.a. contrast administration
I (intervention)	discontinuation of metformin or reduction of metformin-dose
C (comparison)	continuation of metformin
O (outcome)	metformin associated lactate acidosis and risk of serious hyperglycaemia

Relevant outcome measures

The working group considered lactate acidosis and risk of serious hyperglycaemia as critical outcome measures for the decision making process. The working group defined serious hyperglycaemia as a blood glucose level >15mmol/l.

Search and select (method)

The data bases Medline (OVID), Embase and the Cochrane Library were searched from January 2000 up to April 2017 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). The literature search procured 211 hits.

Studies were selected based on the following criteria:

- adult patients who underwent radiological examination using contrast media (including radiological examination during percutaneous angiography);
- patients with impaired kidney function, at least eGFR <60 ml/min/1,73m²;
- hydration types: hydration with NaCl, hydration with bicarbonate, oral hydration, pre-hydration, pre- and posthydration;
- at least one of the outcome measures was described: metformin associated lactate acidosis, risk of serious hyperglycaemia.

Based on title and abstract a total of 62 studies were selected. After examination of full text a total of 60 studies were excluded and 1 study definitely included in the literature summary. This was a systematic review of guidelines and original articles (Georgen, 2010) that examined our research question.

Results

Studies were included in the literature analysis, the most important study characteristics and results were included in the evidence tables. The evidence tables and assessment of individual study quality are included

Summary of literature

Description of studies

One systematic review (Georgen, 2010) was identified that examined the question whether metformin was related to lactic acidosis after administration of intravascular contrast medium for radiological research. Georgen (2010) performed a literature search from 1970 onward to March 2009. This systematic review included the evidence base of 5 frequently cited guidelines that consisted of RCTs, observational studies, case series and case reports. A total of 4 studies were deemed eligible and included in the review.

Results

Georgen, 2010 found a total of 4 studies, 2 summaries of published case-reports (McCartney, 1999; Stades, 2004), one case-series (Nawaz, 1998) and 1 case-report (Jain, 2008). The studies were deemed of insufficient quality to provide evidence to answer our research question due to their study design.

Quality of evidence

A quality of evidence could not be determined, since no original studies were found in this search, or in the included systematic review, that answered the research question appropriately.

Conclusions

	<p>It is not clear whether cessation of metformin in patients undergoing intravascular contrast administration for radiological examination is effective for decreasing the risk of metformin-associated lactic acidosis and hyperglycaemia.</p> <p><i>(Georgen, 2010)</i></p>
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Considerations

Metformin is the most frequently used oral glucose-lowering drug in patients with diabetes mellitus type 2 (DM2). Reduced hepatic glucose production and increased insulin sensitivity are major mechanisms of its anti-hyperglycaemic effect (Lalau, 2015). Metformin inhibits the mitochondrial respiratory chain, impairing the main site of energy generation through aerobic metabolism. This results in a shift toward anaerobic metabolism with lactate as a by-product and less energy for gluconeogenesis. Compared to DM2 patients taking other glucose-lowering drugs, metformin users have reported somewhat higher serum lactate levels, but almost always within the normal range (Liu, 2009; Mongraw-Chaffin). However, in other studies no association between metformin use and serum lactate levels could be established (Lim, 2007; Connolly, 1996).

Lactic acidosis is an anion-gap metabolic acidosis defined by serum lactate levels greater than 5 mmol/l and pH less than 7.35 and is a feared complication of the use of metformin. Severe lactic acidosis causes multisystem organ disorder, particularly neurologic (stupor, coma, seizures) and cardiovascular (hypotension, ventricular fibrillation) dysfunction, and carries a >50% mortality risk. There is no evidence that in patients with a normal kidney function metformin use is associated with an increased risk of lactic acidosis (Inzucchi, 2014). In patients with impaired kidney function, metformin levels increase if the dose of metformin is not reduced, potentially increasing the risk of lactic acidosis. However, case-reports of lactic acidosis in patients taking metformin indicate that lactic acidosis in most cases is unrelated to plasma metformin levels, challenging the concept of a causal relation between metformin use and the occurrence of lactic acidosis (Inzucchi, 2014). Zeller, 2016 included 89 patients not using metformin and 31 patients using metformin with an eGFR <60 ml/min/1.73m². The mean eGFR in the metformin users was 48±10 ml/min. Acute kidney injury following the PCI procedure occurred in 41% of patients versus in 40% of non-metformin users. No case of lactic acidosis during hospital stay was observed. Lactic acidosis solely induced by metformin use is exceptionally rare. In patients who develop lactic acidosis, while using metformin, other comorbidities such as infection, acute kidney or liver failure or cardiac failure are almost always present. These comorbidities are supposed to play a central role in the aetiology of lactic acidosis in metformin users. Therefore, metformin-associated lactic acidosis (MALA) is a more appropriate term than the term metformin-induced lactic acidosis (Lalau, 2015).

Metformin is cleared by the kidney and eliminated unchanged in the urine. This drug may therefore accumulate in patients with impaired kidney function as can occur in response to administration of iodine-containing CM. Below which level of kidney function metformin should no longer be described is open to discussion.

Until very recently, the advice was not to prescribe metformin in patients with an eGFR <60 ml/min/1.73 m². Based on the available literature, a recent report in the JAMA suggests that metformin prescription at a reduced dose of maximal 1000 mg per day can be considered in patients with a CKD grade 3A (eGFR 45-59 ml/min/1.73m²), unless kidney function is expected to become unstable (Inzucchi, 2014). In accordance with this suggestion, the FDA Drug Safety Communication recently has revised warnings regarding the use of metformin in patients with reduced kidney function (FDA website). According to this guideline metformin is contraindicated in patients with an eGFR <30 ml/min/1.73m² and starting metformin in patients with an eGFR between 30 and 44 ml/min/1.73m² is not recommended, but no longer contraindicated. In addition, it is advised to discontinue metformin at the time of or before an iodine-containing contrast imaging procedure in patients with an eGFR between 30 to 60 ml/min/1.73 m². The eGFR should be re-evaluated 48 hours after the imaging procedure and metformin can be restarted if renal function is stable.

The guideline released by the CMSC of the ESUR (version 9.0, 2014) for patients taking metformin is more liberal. Patients with an eGFR ≥ 45 ml/min/1.73 m² receiving i.v. iodine-containing CM can continue to take metformin, whereas patients receiving i.v. or i.a. CM with an eGFR between 30 and 44 ml/min/1.73 m² should stop metformin 48 h before iodine-containing CM administration and should only restart metformin 48 h after CM if renal function has not deteriorated. No advice is given for patients on metformin receiving i.a. contrast who have an eGFR 45 to 59 ml/min/1.73 m². In agreement with the FDA guideline metformin is contraindicated in patients with an eGFR <30 ml/min/1.73 m².

Goergen, 2010 has performed a systematic review of five guidelines and their underlying evidence concerning the risk of lactic acidosis after administration of iodine-containing CM. For their evaluation the authors used the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument. The following five guidelines were assessed: The American College of Radiology (ACR), the Royal Australian and New Zealand College of Radiologists (RANZCR), the British Royal College of Radiologists (RCR), the Canadian Association of Radiologists (CAR) and the European Society of Urogenital Radiology (ESUR).

Comparison of these guidelines with regard to recommendations about CM administration revealed inconsistency between and lack of clarity within many of the guidelines.

The authors of this systematic review conclude:

- a) that there are inconsistencies between the recommendations of the five international guidelines about CM administration in patients taking metformin and;
- b) that these inconsistencies are in part caused by the low level or lack of evidence underlining guideline recommendations.

When translating their finding into implications for patient care, the conclusion of the authors is that there is no increased risk of lactic acidosis in patients taking metformin who have a stable normal renal function, obviating the need to stop taking metformin before iodine-containing CM administration.

In our systematic search and appraisal of the literature no studies could be found that provide any high quality evidence concerning our question about the continuation or discontinuation of metformin in relation to eGFR in patients undergoing radiologic examination with CM. As consequence only expert opinion-based recommendations can be given. It is the opinion of the workgroup that in patients with an eGFR ≥ 30 ml/min/1.73m² the disadvantage of discontinuation of metformin with respect to the development of hyperglycaemia and administrative procedures does not weigh against its continuation as the chance of developing PC-AKI in these patients is negligibly low when the usual preventive measures like prehydration (see Hydration chapter 6) are taken.

Since the chance of kidney function deterioration with intravenous CM administration is neglectably low, metformin (in appropriate dose) can be continued.

In situations where the chance of kidney deterioration is greater, it is the advice of the working group to discontinue metformin immediately before the procedure and to inform the physician who requested the procedure with intravascular contrast. According to the FDA guidelines metformin should always be discontinued in patients with an eGFR < 30 ml/min/1.73 m².

Recommendation

Continue metformin in all patients with an eGFR ≥ 30 ml/min/1.73m² scheduled for imaging to whom intravascular iodine-containing contrast medium is administrated.

Discontinue metformin in all patients with an eGFR < 30 ml/min/1.73m² to whom intravascular iodine-containing contrast medium is administrated as soon as this level of kidney dysfunction is detected and inform the requesting and prescribing physician.

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Chapter 9 Organization of Health Care

When compared to the CBO 2007 guideline on iodine-containing contrast media, several recommendations have been revised. Overall, the most important changes involve: an improved terminology and PC-AKI definition, a lower threshold of eGFR for hydration indication, another type of hydration (bicarbonate) as a recommended preventive measure and a conservative attitude towards preventive measures for PC-AKI other than hydration. To enhance the implementation of this guideline, changes in the organizational structure are recommended as described in the paragraphs below.

Electronic medical records

In the Netherlands, different electronic medical records (EMR) or Hospital Information Systems (HIS) are available from different vendors.

We strongly recommend the same manner of implementation of this guideline, with at least:

- application forms with eGFR, in combination with a medication order for intravascular contrast medium and a medication order for hydration;
- in the medication list, an overview of the administered intravascular contrast media;
- a query regarding all imaging studies / procedures with intravascular iodine-containing contrast media, eGFR and administered hydration;

Hospital-based protocol

For optimal implementation of this guideline a hospital-based protocol describing preventive measures, workflow and responsibilities should be designed. This protocol should be determined by a panel of various experts (including at least a nephrologist, an (vascular) internist, a pharmacist, a cardiologist, a radiologist, a CT or an Angiography technologist, and a quality assurance officer).

The referring physician is responsible for analysing and giving notice of the patient's kidney function, instructing about the patient's medication, and instructing on the administration of hydration and the patient's after-care. The decision on contrast administration should be taken by the physician (radiologist, cardiologist, etc.) responsible for the diagnostic or interventional procedure. Actions can be delegated to others according to local rules and protocols. For example, patients at risk can be referred to a nephrology outpatient clinic (or even a "CI-AKI Prevention Clinic"). This has the advantage of a broader expertise and a better data acquisition.

Workflow and responsibilities

Responsible person	Action and responsibility
Referring physician	Order procedure: contrast enhanced CT (ceCT), angiography / intervention Discuss alternative imaging with the physician responsible for procedure, if indicated Inform patient about procedure Determine eGFR Assess patient's hydration status Assess necessity of preventive measures - hydration Instruct patient about medication (stop or continue) metformin / nephrotoxic drugs Instruct patient about fluid intake Arrange hospital admission for hydration

	Order hydration in patient record
Physician responsible for the procedure - Cardiologist / Radiologist / Nuclear Medicine specialist / Radiotherapist	Check order procedure Discuss alternative imaging with referring physician, if indicated Check eGFR Check hydration Determine procedure protocol and choice of intravascular contrast medium In case of disagreement, consult referring physician Order contrast medium in patient record
Referring physician	<i>Before procedure:</i> Administrate hydration Record hydration in patient record (type/name, concentration, volume, duration) <i>After procedure:</i> check eGFR If PC-AKI, then treatment and follow-up and record PC-AKI in patient record
Physician responsible for the procedure	<i>Before and during procedure:</i> Check eGFR and check whether hydration is administered correctly Check contraindications for CM administration Administer contrast medium Record contrast administration in patient record (name, concentration, volume)

Exceptions

Emergency patients / procedures

In case of a major life-threatening medical condition requiring rapid decision-making including emergency imaging or intervention (e.g. stroke), the determination of the eGFR can be postponed or the imaging or intervention can be started while the eGFR is being determined in the laboratory. If the possibility exists to wait a short time before commencing diagnosis or intervention, without doing harm to the patient, eGFR should be determined immediately, and if indicated, individualized preventive measures should be taken before the administration of intravascular iodine-containing contrast medium.

Kidney transplant recipients

Caution is advised in kidney transplant recipients, because of the lack of good scientific research related to intravascular iodine-containing contrast administration in this group. Considering an alternative imaging modality (e.g. MRI or ultrasound with or without contrast media) is advisable.

Optimal nephrology care should always be mandatory. If iodine-containing contrast medium needs to be given in patients with an eGFR < 30 ml/min/1.73m², preventive hydration is advised, and when necessary individualized to the condition of the patient. For elective examinations, consultation of a nephrologist is recommended.

General safety issues

Hydration situation

Optimal nephrology care is mandatory. Dehydration of patients before intravascular contrast administration is undesirable and should be avoided or corrected by giving normal saline or Ringer's lactate.

Alternative methods of investigation

In patients with severe renal failure, the need for the use of contrast medium should be re-examined. Some diagnoses may just as well be made with other potential imaging modalities, like MRI or ultrasound, or by performing an unenhanced study. CO₂

angiography may be an alternative to angiography with intravascular iodine-containing contrast medium.

Contrast media

The dose of iodine-containing contrast medium should be minimized without compromising the diagnostic aspect of the study/procedure, taking into consideration the indication and the patient's body weight. In angiography / interventional procedures the amount of contrast medium used is highly variable. There must always be a commitment to use the lowest possible dose of contrast medium.

With the development of new generations of CT scanners and angiography equipment, and improved contrast media injection systems, the total volume of contrast medium used for most contrast-enhanced CT /angiography studies has dropped. Also, lower tube voltages allow for lower volumes of CM as lower tube voltage give more signal/ml CM.

Consecutive procedures in a patient

Multiple procedures with intravascular iodine-containing contrast medium within 24 hours should be avoided when possible, and only performed when strictly indicated. There are no strict maximum permissible doses of contrast, but in general volumes of over 250-300 cc in a 24-hour period should be avoided.

In addition, one must realize that intravascular iodine-containing contrast medium is used in contrast-enhanced CT, PET/CT scans with diagnostic contrast-enhanced CT, and angiography / interventional procedures at the departments of cardiology and radiology.

Information and registration

Patient information

Appropriate patient information leaflets should be available, both about the investigational method applied and about the preventive hydration procedure. One should consider having these available in multiple languages.

Patient checklist for contrast medium

Consider a checklist for outpatients to check essential information directly before administration of intravascular iodine-containing contrast media. The checklist should include: impaired renal function, dialysis, diabetes mellitus, metformin therapy, and previous hypersensitivity reaction to contrast media.

Registration of the contrast medium

Intravascular contrast administration (agent name, concentration, volume) should be recorded in 2 ways:

- A. Patient record
- B. On the CT images

The correct information about contrast medium - agent name, concentration and volume in ml - on the CT images will ensure optimal transparency, both in the hospital

where the CT images are performed and in any other hospital to which the patient might have been referred.

Chapter 10 Implementation table

Implementation Plan

This implementation plan has been formulated to improve the implementation of the guideline Safe Use of Contrast Media, part 1. In the preparation of this plan an inventory has been made of the promoting and limiting factors in the use of the recommendations. The working group of this guideline advised on the time path for its implementation and the specific actions that need to be performed by the various stakeholders.

Methods

The Working Group has made an inventory for each of its (strong) recommendations:

- When the recommendations can be implemented in all hospitals.
- The expected impact of implementation of the recommendation on hospital costs.
- Limiting conditions to implementation of recommendations.
- Barriers to implementation of recommendations.
- Actions to promote implementation of recommendations.
- Identification of the parties that are responsible for such actions.

Not every item could be answered for every individual recommendation. There are weakly and strongly formulated recommendations. For the weakly formulated recommendations there is more room for alternative options. The inventory is done more completely for strongly formulated recommendations.

Implementation Timeline

Strongly formulated recommendations are generally implemented in a short time, for instance in the coming 12 months. This means that these are to be implemented before August 1st, 2018.

As there was a great demand for the revision of the Prevention of CI-AKI part of this guideline by the entire Dutch medical community, it is expected that implementation may proceed quite swiftly.

Impact on Healthcare Costs

Many recommendations have no, limited or positive consequences for healthcare costs.

The reduction in the number of patients that need preventive hydration as well as the short hydration protocol that does not need to be performed anymore in an expensive day hospital setting will have a positive effect on the reduction of healthcare costs.

A detailed summary of the recommendations and the details of their effects on healthcare cost are shown below in Table 10.1.

Specific Actions for Stakeholders

The actions which need to be taken by stakeholders are listed below.

The primary responsible scientific society (Radiology, NVvR):

- Distribution of this guideline text among its members, via all NVvR sections.
- Publication of a summary of this guideline in a peer-reviewed medical journal and on the society's website NetRad (www.radiologen.nl).
- Sharing of this guideline with their European sister organisations.
- Sharing of this guideline with influential contrast media safety guideline committees from the European Society of Urogenital Radiology (ESUR), American College of Radiology (ACR), Canadian Association of Radiologists (CAR), Royal Australian and New Zealand College of Radiology (RANZCR), and Japan Radiological Society (JRS).
- Checking the implementation of the recommendations of this guideline via specific audits and the routine quality visitation system of radiology groups.
- Creation of a continuous modular maintenance system for this guideline and its sub guidelines.

All other directly involved scientific societies (NFN, NIV, NVVC, NVVH, NVIC, NVKC, etc.):

- Distribution of this guideline text among its members.
- Checking the implementation of the recommendations of this guideline via audits and the quality visitation system.
- Creation of a continuous modular maintenance system for this guideline and its sub guidelines.

All local MSBs, specialist groups or individual medical professionals:

- Distribution this guideline text among its members or in local working groups.
- Adaptation of local patient information based on the information in this guideline.
- Discussion with other involved specialities to come to a system to implement the guideline recommendations in local practices.

Healthcare system stakeholders (like the insurance companies, (organisations of) hospital administrators, Healthcare Inspection):

- It is expected from hospital administrations that they reserve financial means for implementation of this guideline in their Hospital Information System and in local quality systems. In addition, it is expected from insurance companies that they compensate the costs of the care that is detailed in this guideline.

Knowledge Institute of Medical Specialists (KIMS):

- Addition of this guideline to the Dutch Guideline Database (www.richtlijndatabase.nl).
- Inclusion of this implementation plan on easy to find locations.

Table 10.1 Implementation of recommendations

Recommendation	Timeline for implementation <1 year, 1-3 year or 3-5 years	Expected effect on healthcare costs	Boundary conditions for implementation (within the indicated timeline)	Potential barriers for implementation	Actions that need to be undertaken for implementation	Parties responsible for actions	Other remarks
Risk factors							
Optimal nephrology care should be the primary goal in all chronic kidney disease patients, especially with attention to medication-use. Patients with an eGFR <30 ml/min/1.73m ² should be referred to a nephrologist.	<1 year	Cost decrease if patients are referred to a nephrologist on time	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Provide hydration in hypovolemic patients before any examination using intravascular iodine-containing CM.	<1 year	Cost decrease if patients are hydrated when needed – reduces risk of costly complications	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Consult a nephrologist for patients with an eGFR <30 ml/min/1.73m.	1-3 years	Cost decrease if patients are hydrated when needed – reduces risk of costly complications	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
<i>For patients undergoing intravascular iodine-containing contrast medium administration: Consider patients with an eGFR < ml/min/1.73m² at risk for PC-AKI.</i>	1-3 years	Cost decrease if patients are hydrated when needed – reduces risk of costly complications	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals	

						Educators in teaching hospitals	
Apply the same recommendations, indicated for patients with bilateral kidneys, to patients with a solitary kidney subjected to iodine-containing contrast administration.	1-3 years	Cost decrease if patients are hydrated when needed – reduces risk of costly complications	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Consider that low osmolar contrast media and iso-osmolar contrast media have the same safety profile.	1-3 years	Cost decrease if patients are hydrated when needed – reduces risk of costly complications	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Do not use prediction tools to estimate the risk of PC-AKI, since their validity and effect on clinical outcome is unclear.	1-3 years	Cost decrease if patients are hydrated when needed – reduces risk of costly complications	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
eGFR measurement							
Determine eGFR in each patient scheduled for Computed Tomography or Angiography with or without intervention with use of intravascular iodine-containing contrast media. The measurement of eGFR is valid: -For 7 days when the patient has	1-3 years	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	

<p>an acute disease or an acute deterioration of a chronic disease.</p> <p>-For 3 months when the patient has a known chronic disease with stable renal function.</p> <p>-For 12-13 months when the patient was previously healthy.</p>							
<p>Determine eGFR within 2-7 days <i>after</i> intravascular contrast administration in every patient for whom preventive measures against PC-AKI were taken.</p>	1-3 years	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
<p>If PC-AKI is diagnosed (by KDIGO criteria), follow the patient for at least 30 days post-diagnosis and re-assess serum creatinine.</p>	1-3 years	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
<p>Measure the serum or plasma creatinine using a selective (enzymatic) method.</p>	1-3 years	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
<p>Implement the creatinine based CKD-EPI formula for estimation of the eGFR.</p>	1-3 years	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group	

						Hospitals Educators in teaching hospitals	
Consider correcting the eGFR for BSA in the CKD-EPI formula in case that the patient specific body surface area (BSA) is known.	1-3 years	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Optimal hydration strategy							
<i>For patients undergoing intravascular administration of iodine-containing medium with an eGFR <30 mL/min/1.73m² either one of the following options can be used:</i> 1) Prehydrate with 3ml/kg/h NaHCO ₃ 1.4% for 1h pre-CM administration 2) Pre- and posthydrate with 3ml/kg/h NaHCO ₃ 1.4% for 1h pre-CM and 1ml/kg/h for 6h post CM administration.	1-3 years	Decrease of healthcare costs is expected, mainly due to decrease in hospital admission time	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Do not use hydration with controlled diuresis for the prevention of PC-AKI in patients undergoing (cardiac) angiography with or without intervention, unless it is performed in a research setting.	1-3 years	Decrease of healthcare costs is expected, mainly due to decrease in hospital admission time	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Do not use oral hydration as the sole means of prevention of PC-AKI.	<1 year	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working	

						group Hospitals Educators in teaching hospitals	
Measures other than hydration to prevent PC-AKI							
Consider giving short term (48 hours) high dose atorvastatin or rosuvastatin in addition to hydration in statin-naïve patients with eGFR <60 ml/min/1.73m ² undergoing coronary angiography with or without percutaneous coronary intervention.	1-3 years	No significant effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Do not use NAC for the prevention of PC-AKI in patients with a normal or impaired (eGFR <60 ml/min/1.73m ²) kidney function.	<1 year	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Do not use vitamin C exclusively for the prevention of PC-AKI in patients with a normal or impaired (eGFR <60 ml/min/1.73m ²) kidney function.	<1 year	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Do not routinely withhold ACE-inhibitors, Angiotensin receptor blockers or diuretics prior to intravascular contrast administration.	<1 year	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in	

						teaching hospitals	
Withhold NSAIDs prior to intravascular iodine-containing contrast medium administration.	<1 year	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
The working group recommends nephrology consultation before administering iodine-containing contrast in patients with eGFR <30 mL/kg/1.73m ² to individualize continuation or discontinuation of ACE-inhibitors, angiotensin II receptor blockers, diuretics or nephrotoxic drugs and weigh this against the potential benefits and harm of the administration of iodine-containing CM.	<1 year	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Do not use prophylactic dialysis in patients with chronic kidney disease stage 4-5 receiving intravascular contrast for coronary angiography with or without percutaneous intervention, to lower the risk of post contrast acute kidney injury.	<1 year	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Do not use prophylactic hemofiltration routinely in patients with chronic kidney disease stage 4-5 receiving intravascular contrast for coronary angiography with or without percutaneous	<1 year	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in	

intervention.						teaching hospitals	
Do not adapt the schedule of chronic dialysis to the performance of a contrast-enhanced imaging study (or in other words: the scheduling of a contrast-enhanced imaging study does not need to be adapted to the dialysis schedule of the patient).	<1 year	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Metformin							
Continue metformin in all patients with an eGFR 30- 44 ml/min/1.73m ² scheduled for imaging to whom intravascular iodine-containing contrast medium is administrated.	1-3 years	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	
Discontinue metformin in all patients with an eGFR ≤30 ml/min/1.73m ² to whom intravascular iodine-containing contrast medium is administrated as soon as this level of kidney dysfunction is detected <i>and inform the requesting physician.</i>	1-3 years	No effect on costs is expected	None expected	Lack of knowledge	Dissemination of guideline	Scientific societies participating in guideline working group Hospitals Educators in teaching hospitals	

Chapter 11 Knowledge Gaps

Overall knowledge gaps

Creation of a National and Regional PC-AKI Registry in the Netherlands

While the number of patients with an impaired renal function CKD grade 4-5, eGFR <30 ml/min/1.73m²) is relatively limited, the nephrology care for these patients should be optimized. This requires an optimal database that is currently lacking. Data are needed on their nephrology status and co-morbidities, but also of their evolution of their renal function impairment, both before and after imaging with intravascular iodine-containing contrast media. A potential type of study design that may provide relevant information is a cluster randomization study where radiologists/cardiologists and nephrologists cooperate.

Such an effort would require data input from multiple hospitals (university and community), organized by a multidisciplinary team of medical specialists from different backgrounds as well as IT-specialists from Hospital Information Systems.

Improved data on CI-AKI from intra-arterial CM

The efforts made in the radiological community to separate CIN from PC-AKI by performing randomized controlled trials and, when possible, propensity score-matched studies with well-matched control populations should be extended to interventional radiology and cardiology. This would allow the evaluation of the epidemiology of “true” CI-AKI in catheter-based diagnostic and interventional studies, and the possible contributory, confounding effects of catheter or device manipulations. However, this is very complex since the definition of good control populations for interventional procedures is not straightforward as sham procedures are never performed. For some vascular territories, CO₂ angiography may be a suitable comparator.

Better stratification of the relative risks of interventional procedures

There is abundant literature about risk of PC-AKI and intra-arterial iodine-containing CM administration in (coronary) angiography including percutaneous (coronary) interventions. However, this is a very heterogeneous patient group, which could be much better stratified in procedures with low/medium/high relative risks depending on the patient characteristics, type and length of the procedure, and/or CM use. In the future, a well validated risk assessment model may become available.

Knowledge gaps per guideline chapter

Risk stratification and stratification tools

- 1) It is unclear which patient-related determinants can predict that intravenous hydration will decrease the risk of PC-AKI.
- 2) It is unclear whether patients with a kidney transplantation have an increased risk of PC-AKI.
- 3) It is unclear which risk stratification tools should be used for the estimation of the risk of PC-AKI in patients undergoing either intravenous or intra-arterial iodine-containing contrast medium administration.

Estimation of Glomerular Filtration Rate

- 1) It is unclear what length of time a serum creatinine or eGFR measurement is valid, when estimating the risk of PC-AKI.
- 2) It is unclear what the optimal follow-up time is for a patient who has developed PC-AKI.

Prevention: hydration and complications

- 1) It is unclear whether the risk of PC-AKI is similar in patients who receive intravenous iodine-containing contrast-medium administration in combination with hydration versus no hydration.
- 2) It is unclear whether controlled hydration is more effective in reducing the risk of PC-AKI as compared to standard hydration in patients who receive intra-arterial iodine-containing contrast medium administration for a coronary angiography with or without intervention.
- 3) It is unclear whether the risk of PC-AKI is similar in patients who receive intravenous iodine-containing contrast medium administration in combination with oral hydration versus standard hydration.
- 4) It is unclear which schedule (of pre- and/or posthydration) is the most optimal hydration schedule to reduce the risk of PC-AKI, both in patients undergoing intravenous iodine-containing contrast medium administration and in patients undergoing intra-arterial iodine-containing contrast medium administration.

Other preventive measures: Statins

- 1) It is unclear which type of statin is optimal to reduce the risk of PC-AKI in patients undergoing intra-arterial iodine-containing contrast medium administration.
- 2) It is unclear which dosing scheme of statin before and/or after hydration is optimal to reduce the risk of PC-AKI.

Other preventive measures: N-acetylcysteine

- 1) It is unclear whether N-acetylcysteine reduces the risk of PC-AKI in patients undergoing intravenous or intra-arterial iodine-containing contrast medium administration.
- 2) It is unclear whether N-acetylcysteine should be administered orally or intravenously to reduce the risk of PC-AKI optimally.
- 3) It is unclear whether any positive effect of N-acetylcysteine on kidney function contributes to true kidney-sparing effects.

Other preventive measures: Vitamin C

- 1) It is unclear whether Vitamin C reduces the risk of PC-AKI in patients undergoing intravenous or intra-arterial iodine-containing contrast medium administration.
- 2) It is unclear which administration route (orally or intravenously) and dose of Vitamin C should be used to optimally reduce the risk of PC-AKI.

Other preventive measures: Discontinuation of nephrotoxic medication

- 1) It is unclear whether discontinuation of any type of nephrotoxic medication prior to intravascular iodine-containing contrast medium administration reduces the risk of PC-AKI in patients that chronically use this medication.

Other preventive measures: Dialysis and hemo(dia)filtration

- 1) It is unclear whether haemodialysis or hemo(dia)filtration reduces the risk of PC-AKI in CKD 4-5 patients undergoing intravascular iodine-containing contrast medium administration.
- 2) It is unclear whether the potential beneficial effects of haemodialysis or hemo(dia)filtration outweigh the risks whether in CKD 4-5 patients undergoing intravascular iodine-containing contrast medium administration.

Contrast medium use in diabetic patients using metformin

- 1) It is unclear whether metformin is the cause of lactic acidosis in patients undergoing intravascular contrast administration.
- 2) It is unclear whether discontinuation of metformin in patients with type 2 diabetes reduces the risk of lactic acidosis in patients undergoing intravascular iodine-containing contrast medium administration.

Chapter 12 Quality Indicators

Introduction

Quality and transparency are important subjects in the organisation of healthcare in 2017. Thus indicators are developed parallel to guidelines to measure quality of healthcare. The Radiological Society of the Netherlands expects that this set of indicators will stimulate professional conduct in radiology, and other medical specialities involved in implementing the guideline Safe Use of Contrast Media, Part 1, to ultimately improve patient care.

The goal of the indicator set is to measure the implementation of the guideline Safe Use of Contrast Media, Part 1 in hospitals.

Types of indicators

Indicators are measurable elements of healthcare that provide information about the quality of the healthcare delivered (Lawrence, 1997). An indicator is a tool for measuring quality. Defining an indicator is the operationalization of what you want to measure. Information needs to be obtained to use an indicator, and a calculation is performed based on this information.

There are three types of indicators: input indicators, process indicators and outcome indicators (Donabedian, 1980). Input indicators provide information about (organisational) conditions within which healthcare is provided. An example of an input indicator is “the presence of a stroke unit in a hospital”. Process indicators provide information about proceedings within a healthcare process. A characteristic of process indicators is that they can be influenced directly: they measure how often something had been done. An example of a process indicator is the percentage of patients with diabetes that receive a yearly ophthalmological examination. Outcome indicators provide information about the outcome of healthcare processes, measured at the patient level. Outcome indicators are often dependent on many factors, and can therefore not be linked directly to quality of patient care. An example of an outcome indicator is the percentage of patients with postoperative infections after a cholecystectomy.

Methods

The guideline working group: Safe use of contrast media part 1, has made a selection of recommendations during several meetings. The recommendations were selected by how they influenced the improvement of quality of healthcare. Afterwards, indicators were defined based on the selected recommendations. The indicators were presented for peer review, together with the rest of the guideline, to all scientific societies and other stake holders involved in the development of the guideline. After revision, the indicators were presented for authorization, together with the rest of the guideline.

Results

This is a set of indicators made by and for medical specialists involved in the treatment of patients who receive intravascular iodine-containing contrast medium. The working group has selected subjects that are most relevant, in the opinion of the working group, to promote implementation of the guideline. These subjects are directly linked to the

recommendations of the guideline Safe use of contrast media – part 1. Furthermore, the indicators can be directly or indirectly influenced by the healthcare providers. Moreover, the indicators should be able to detect differences between hospitals. A mix of indicators has been chosen, on different quality domains that are valid as a measurement for quality of healthcare. The chosen indicators are reliable and valid.

Overview of indicators

Three indicators were developed, one input indicator and two process indicators.

	Indicator	Type
1	Is there an overall hospital -wide protocol or process-agreement on how prevention of PC-AKI is organized for patients with intravascular iodine-containing contrast medium administration?	input
2	Percentage of patients who receive hydration during CT with iodine-containing CM, from all patients with an eGFR<30ml/min/1.73m ² who receive a CT with iv iodine-containing CM.	process
3	Percentage of patients who had an eGFR measurement 3-7 days after CT with iv CM, from all patients with an eGFR<30ml/min/1.73m ² who received a CT with iodine-containing CM and were hydrated preventively.	process

CM: contrast medium; CT: computed tomography; eGFR: estimated Glomerular Filtration Ratio; iv: intravascular; PC-AKI: post-contrast acute kidney injury

The indicators are described in the paragraphs below.

Factsheets of indicators

Hospital-wide protocol availability about prevention of PC-AKI

1. Hospital-wide protocols about prevention of PC-AKI	
Operationalization	Is there an overall hospital -wide protocol or process-agreement on how prevention of PC-AKI is organized for patients with intravascular iodine-containing contrast medium administration available?
Numerator	Not applicable
Denominator	Not applicable
Type of indicator	Input
In- and exclusion criteria	Inclusion A hospital-wide protocol, that applies to all departments of the hospital, for the prevention of iv and ia contrast administration
Quality domain	Safety and effectivity
Measuring frequency	Once a year
Report year	2018
Frequency of report	Once a year

Explanation

Background and variation in healthcare

The goal of this indicator is to stimulate hospitals to make hospital-wide agreements and protocols for the prevention of PC-AKI, (e.g. hydration) for patients that receive intravascular iodine-containing CM. In current clinical practice some hospitals have separate protocols in different departments (Radiology and Cardiology, for example), so patients may receive different hydration schemes.

Definitions

PC-AKI: post contrast acute kidney injury – see introduction and definitions chapters of the guideline.

Iv: intravascular – see introduction and definitions chapters of the guideline.

Practical implications

This is an input indicator that can be answered once a year by “yes” or “no” per hospital. It takes several minutes to register this indicator. The working group believes that the burden of registration outweighs the potential quality improvement that can be achieved by this indicator.

Potential confounders.

The working group does not expect that case-mix or bias might occur while measuring this input indicator.

Potential unwanted effects

The working group does not expect that unwanted effects might occur while measuring this input indicator.

Percentage of patients that undergo a CT-scan with iodine-containing CM and are hydrated correctly

2. Percentage of patients that undergo a CT-scan with iodine-containing CM and is hydrated correctly	
Operationalization	Percentage of patients who receive hydration during CT with intravascular iodine-containing CM, from all patients with an eGFR <30ml/min/1.73m ² who receive a CT with iv iodine-containing CM.
Numerator	Number of patients with an eGFR <30ml/min/1.73m ² who receive preventive hydration during CT with intravascular iodine-containing CM
Denominator	All patients with an eGFR <30ml/min/1.73m ² who receive a CT with intravascular iodine-containing CM
Type of indicator	Process indicator
In- and exclusion criteria	Inclusion: -patients for whom a CT-scan with iodine-containing intravascular CM is indicated -eGFR<30 ml/min/1.73m ² Exclusion: -patients with acute life-threatening conditions, when there is no time to perform an eGFR measurement prior to CM administration. This should be recorded in the patient file. -patients who refused an eGFR measurement or preventive hydration. This should be recorded in the patient file. -dialysis patients without rest diuresis.
Quality domain	Safety and effectivity
Measuring frequency	Once per 3 months
Report year	2018
Frequency of report	Once per year

Explanation

Background and variation in healthcare

The goal of this indicator is to measure whether all patients who receive a CT-scan with iodine-containing iv CM and in whom preventive hydration is indicated, actually receive this hydration in a correct fashion.

Definitions

PC-AKI: post contrast acute kidney injury – see introduction and definitions chapters of the guideline.

Iv: intravascular – see introduction and definitions chapters of the guideline.

Practical implications

The data for this indicator can be extracted from the electronic patient files. The working group believes that the burden of registration outweighs the potential quality improvement that can be achieved by this indicator.

Potential confounders

The working group does not expect that case-mix or bias might occur while measuring this input indicator.

Potential unwanted effects

The working group does not expect that unwanted effects might occur while measuring this input indicator.

Post-contrast kidney function check in all patients who received hydration

3. Post-contrast kidney function check in all patients who received hydration prior to CT-scan	
Operationalization	Percentage of patients who were checked by an eGFR measurement 3-7 days after CT with iv CM, from all patients with an eGFR<30ml/min/1.73m ² who received a CT with intravascular iodine-containing CM and were hydrated preventively.
Numerator	Number of patients with an eGFR <30ml/min/1.73m ² who were checked by an eGFR measurement 3-7 days after preventive hydration for CT-scan with intravascular iodine-containing CM
Denominator	All patients with an eGFR <30ml/min/1.73m ² who receive preventive hydration for CT-scan with intravascular iodine-containing CM
Type of indicator	Process indicator
In- and exclusion criteria	Inclusion: -patients in whom a CT-scan with iodine-containing intravascular CM is indicated -eGFR<30 ml/min/1.73m ² Exclusion: -patients with acute life-threatening conditions, when there is no time to perform an eGFR measurement prior to CM administration. This should be recorded in the patient file. -patients who refused an eGFR measurement or preventive hydration. This should be recorded in the patient file. -dialysis patients without rest diuresis
Quality domain	Safety and effectivity
Measuring frequency	Once per 3 months
Report year	2018
Frequency of report	Once per year

Explanation

Background and variation in healthcare

The goal of this indicator is to measure whether all the patients who received preventive hydration receive the correct aftercare.

Definitions

PC-AKI: post contrast acute kidney injury – see introduction and definitions chapters of the guideline.

Iv: intra-vascular – see introduction and definitions chapters of the guideline.

Practical implications

The data for this indicator can be extracted from the electronic patient files. The working group believes that the burden of registration outweighs the potential quality improvement that can be achieved by this indicator.

Potential confounders

The working group does not expect that case-mix or bias might occur while measuring this input indicator.

Potential unwanted effects

The working group does not expect that unwanted effects might occur while measuring this input indicator.

References

Donabedian, A. Explorations in Quality Assessment and Monitoring Vol. 1. The Definition of Quality and Approaches to Its Assessment. Ann Arbor, MI: Health Administration Press, 1980

English summary of recommendations

Below is a summary of the recommendations from multidisciplinary evidence-based clinical guideline Safe Use of Contrast Media, part 1. This guideline encompasses the indications and measures to prevent post-contrast acute kidney injury (PC-AKI) when iodine-containing contrast media are being administered. It also gives guidance for the use of contrast media in patients with type 2 diabetes that use metformin and on the use of contrast media in patients that undergo chronic dialysis.

In this summary the scientific evidence and the considerations which have led to these recommendations are missing. For this information the full guideline needs to be consulted. This summary of recommendations should not be used alone. In medical decision making the personal setting and preferences of the patient should be taken into consideration. Treatment and procedures of the individual patient rely on mutual communication between patient, physician en other caregivers.

Chapter 4

How can patients with an increased risk of post-contrast acute kidney injury (PC-AKI) from examinations with injection of intravascular iodine-containing contrast media be identified?

Aim for clinical euvolemia, using normal saline or Ringer's lactate, before administration of intravascular iodine-containing CM, regardless of eGFR.

For patients undergoing intravascular administration of iodine-containing CM: Consider patients with an eGFR <30 ml/min/1.73m² at risk for PC-AKI.

Apply the same recommendations, indicated for patients with bilateral kidneys, to patients with a solitary kidney or kidney transplantation subjected to iodine-containing contrast administration.

Consider that low osmolar contrast media and iso-osmolar contrast media have the same renal safety profile.

Optimal nephrology care should be the primary goal in all chronic kidney disease patients, especially with attention to hydration status and medication use.

Consider an alternative imaging technique that does not require iodine-containing CM in all patients with an increased risk of PC-AKI.

Consult a nephrologist/internist for patients with an eGFR <30 ml/min/1.73m².

Do not use prediction models or questionnaires to estimate the risk of PC-AKI, since their validity and effect on clinical outcome is unclear.

Chapter 5

How should renal function be measured before and after administration of iodine-containing contrast medium?

Recommendations for physicians requesting laboratory diagnosis

Determine eGFR in each patient scheduled for Computed Tomography or Angiography with or without intervention with use of intravascular iodine-containing contrast media prior to CM administration.

The measurement of eGFR is valid for:

- maximally 7 days when the patient has an acute disease or an acute deterioration of a chronic disease;
- maximally 3 months when the patient has a known chronic disease with stable renal function;
- approx. 12 months in all other patients.

Determine eGFR within 2 to 7 days after intravascular contrast administration in every patient for whom preventive measures against PC-AKI were taken.

If PC-AKI is diagnosed (by KDIGO criteria), follow the patient for at least 30 days post-diagnosis and re-assess serum creatinine.

Recommendations for the clinical chemist

Measure the serum or plasma creatinine using a selective (enzymatic) method.

Implement the creatinine based CKD-EPI formula for estimation of the eGFR.

Consider correcting the eGFR for BSA in the CKD-EPI formula in case that the patient's specific body surface area (BSA) is known.

Chapter 6

Which preventive hydration strategy should be implemented for patients with an increased risk for PC-AKI that will undergo examination with intravascular administration of iodine-containing contrast media?

For patients with an eGFR <30 ml/min/1,73m² undergoing intravascular administration of iodine-containing contrast medium either one of the following hydration regimens can be used:

- prehydrate with 3ml/kg/h NaHCO₃ 1.4% for 1h (or a total of 250ml) pre-CM administration;
- pre- and posthydrate with 3ml/kg/h NaHCO₃ 1.4% for 1h (or a total of 250ml) pre-CM and 1ml/kg/h for 6h (or a total of 500ml) post-CM administration

Do not use hydration with controlled diuresis for the prevention of PC-AKI in patients undergoing (cardiac) angiography with or without intervention, unless it is performed in

a research setting.

Do not use oral hydration as the sole means of prevention of PC-AKI.

Chapter 7

Should statins on top of hydration be recommended to lower the risk of PC-AKI in patients with chronic kidney disease that are scheduled for intravascular iodine-containing contrast media?

Consider giving short term (48 hours) high dose atorvastatin or rosuvastatin in addition to hydration in statin-naïve patients with eGFR <60 ml/min/1.73m² undergoing coronary angiography with or without percutaneous coronary intervention.

Should prophylactic N-acetylcysteine on top of hydration be recommended to lower the risk of PC-AKI in patients with normal renal function or chronic kidney disease that are scheduled for intravascular iodine-containing contrast media?

Do not use NAC for the prevention of PC-AKI in patients with a normal or impaired (eGFR <60 ml/min/1,73m²) kidney function.

Should prophylactic Vitamin C on top of hydration be recommended to lower the risk of PC-AKI in patients with normal renal function or chronic kidney disease that are scheduled for intravascular iodine-containing contrast media?

Do not use vitamin C exclusively for the prevention of PC-AKI in patients with a normal or impaired (eGFR <60 ml/min/1,73m²) kidney function.

Should nephrotoxic medication be withheld prior to intravascular administration of iodine-containing contrast media to lower the risk of PC-AKI?

Do not routinely withhold ACE-inhibitors, angiotensin II receptor blockers or diuretics prior to intravascular iodine-containing contrast administration. iodine-containing

Withhold NSAIDs prior to intravascular administration of iodine-containing contrast media

The working group recommends nephrology consultation before administering iodine-containing contrast in patients with eGFR <30 ml/kg/1.73m² to individualize continuation or discontinuation of ACE inhibitors, angiotensin II receptor blockers, diuretics or nephrotoxic drugs and to weigh this against the potential benefits and harm of the administration of iodine-containing CM

Should prophylactic renal replacement therapy be recommended to lower the risk of PC-AKI in patients with chronic kidney disease stage 4-5 that are scheduled for intravascular administration of iodine-containing contrast media during coronary angiography with or without intervention?

Do not use prophylactic dialysis in patients with chronic kidney disease stage 4 to 5

receiving intravascular iodine-containing contrast medium for coronary angiography with or without percutaneous intervention, to lower the risk of post contrast acute kidney injury.

Do not use prophylactic hemofiltration routinely in patients with chronic kidney disease stage 4 to 5 receiving intravascular iodine-containing contrast medium for coronary angiography with or without percutaneous intervention.

The scheduling of an iodine-containing contrast-enhanced imaging study does not need to be adapted to the dialysis schedule of the patient (in other words: do not change the schedule of chronic dialysis for the purpose of a iodine-containing contrast-enhanced imaging study).

Chapter 8

Should metformin be withheld to prevent metformin-associated lactic acidosis (MALA) in patients with chronic kidney disease scheduled for intravascular administration of iodine-containing contrast media?

Continue metformin in all patients with an eGFR 30-44 ml/min/1.73m² scheduled for imaging to whom intravascular iodine-containing contrast medium is administered.

Discontinue metformin in all patients with an eGFR < 30 ml/min/1.73m² to whom intravascular iodine-containing contrast medium is administered as soon as this level of kidney dysfunction is detected and inform the requesting and prescribing physician.

Patient Summary

This guideline includes the following topics:

1. prevention of post-contrast acute kidney injury;
2. use of contrast media in patients with diabetes type 2, using metformin;
3. use of contrast media in chronic dialysis patients.

What is post-contrast acute kidney injury?

Post-contrast acute kidney injury (PC-AKI) is an acute (deterioration of) kidney function that occurs within 48 to 72 hours after administration of iodine-containing contrast media in diagnostic imaging. Until recently this was called Contrast-Induced Acute Kidney Injury (CI-AKI) or Contrast-Induced Nephropathy (CIN).

What is the intended audience of this guideline?

This guideline is applicable to all individuals 18 years and older scheduled for imaging or interventional procedures, into whom iodine-containing contrast media will be injected into the blood vessels. Specific recommendations are given for:

- individuals with severe impaired renal function (eGFR<30ml/min/1.73m²);
- chronic dialysis patients;
- individuals with type 2 diabetes mellitus who use metformin;

Which types of contrast media are covered?

Iodine-containing contrast media that are injected intravenously or through a catheter into the blood vessels for radiographic, vascular diagnostic examination or for vascular or non-vascular treatment, such as:

- CT examinations (Computed Tomography); for a variety of indications;
- (Coronary) Angiography; examinations of the heart or blood vessels;
- Interventions to the heart and blood vessels, like balloon dilatation, placement of metallic stents, or placement of prosthetic heart valves.

This guideline does **not** apply to:

- contrast media for the bowel taken by mouth (orally) or administered rectally;
- contrast media that are injected into joints (intra-articular);
- contrast agents for MRI examinations (Magnetic Resonance Imaging);
- contrast agents for US examinations (Ultrasound);
- radioactive tracers administered for NM examinations (Nuclear Medicine).

Prevention of post-contrast acute kidney injury

Which patients have an increased risk for developing post-contrast acute kidney injury?

When your physician schedules diagnostic or interventional examination with iodine-containing contrast medium your renal function will be evaluated. Based on the results of the serum creatinine value and the so-called estimated glomerular filtration (eGFR) rate which is calculated from serum creatinine, the following patients have an increased risk for developing PC-AKI:

- Patients who are scheduled for a diagnostic or interventional examination with intravascular injection of an iodine-containing contrast medium in the veins or arteries who have a severely reduced renal function (eGFR < 30ml/min/1.73m²), irrespective whether you have one or two kidneys or a kidney transplant.
- If you have a recently diagnosed known acute kidney injury.

How is renal function measured?

The eGFR is calculated from measured creatinine in blood serum or plasma. After scheduling the examination you will have to visit the laboratory for a blood draw. Sometimes creatinine levels have been measured in the past which can be used to monitor progression and if you are eligible for measures to prevent PC-AKI.

How long a renal function test remains valid largely depends on your clinical condition:

- When you are acutely ill, have an acute deterioration of a chronic illness, or when you have been admitted to the hospital, the creatinine measurement is valid for a maximum of 7 days.
- When you have a chronic illness with stable renal function, the creatinine measurement is valid for a maximum of 3 months.
- In all other cases, or when you were previously healthy, the creatinine measurement is valid for approximately 12 months.

How can post-contrast acute kidney injury be prevented?

If you have an increased risk to develop PC-AKI, then preventive hydration can be useful. You will be admitted a few hours before your examination and will get an intravenous line. Via this line 250ml fluids will be administered into your circulation in 1 hour. Your physician can choose, after consulting with you, to give a larger volume of fluids. In that case the fluid administration will continue for 6 hours after the examination, in which you will get another 500ml fluids.

When you have a severely reduced renal function (eGFR < 30ml/min/1,73m²), it is recommended that your physician consults an internal medicine specialist or nephrologist (a kidney specialist) when scheduling an examination with iodine-containing contrast media.

When you have an increased risk for PC-AKI and have received preventive hydration, your physician will check your blood creatinine value after the examination to evaluate whether PC-AKI has occurred or not. For this, your blood needs to be drawn 2 to 7 days after the examination. When your renal function has deteriorated, you will be sent to a nephrologist for renal function monitoring and prevention of further kidney function decline if possible. In most instances, your renal function will recover spontaneously to the preexistent value.

Are there exceptions?

Exception 1: if there is a life-threatening emergency (e.g. stroke, trauma or myocardial infarction), there may be no time to measure and evaluate your renal function before a diagnostic or interventional examination for which iodine-containing contrast media is necessary. In that case the renal function will be evaluated during or shortly after the procedure.

Exception 2: Sometimes you are scheduled for an examination with iodine-containing contrast media while you are hypovolemic or have signs of dehydration (too low fluid-level in the blood vessels or body). Hypovolemia should always be corrected via fluids via the intravenous line, irrespective of the level of your serum creatinine.

I have a kidney transplant. Does this make a difference?

There is no indication to treat a patient with a kidney transplant different from other patients. When your kidney function is more than $eGFR \geq 30 \text{ ml/min/1.73m}^2$, preventive hydration is not necessary. In all cases of severe renal function loss ($eGFR < 30 \text{ ml/min/1.73m}^2$) preventive hydration is indicated.

Use of iodine-containing contrast media in patients on chronic dialysis

Your physician will consult your nephrologist about preventive measures, especially when there is still residual renal function. In general preventive measures will be individualized in your case. Excessive hydration is discouraged prior to or after the administration of iodine-containing contrast media to avoid hypervolemia or congestion. The kidney is already very severely damaged, and the weakly nephrotoxic contrast medium will add little damage to that.

It is not necessary to adapt the timing of an examination with iodine containing contrast media to your weekly dialysis schedule. Also, there is no indication to adapt the dialysis schedule to a gift of iodine-containing contrast medium during a diagnostic or interventional examination.

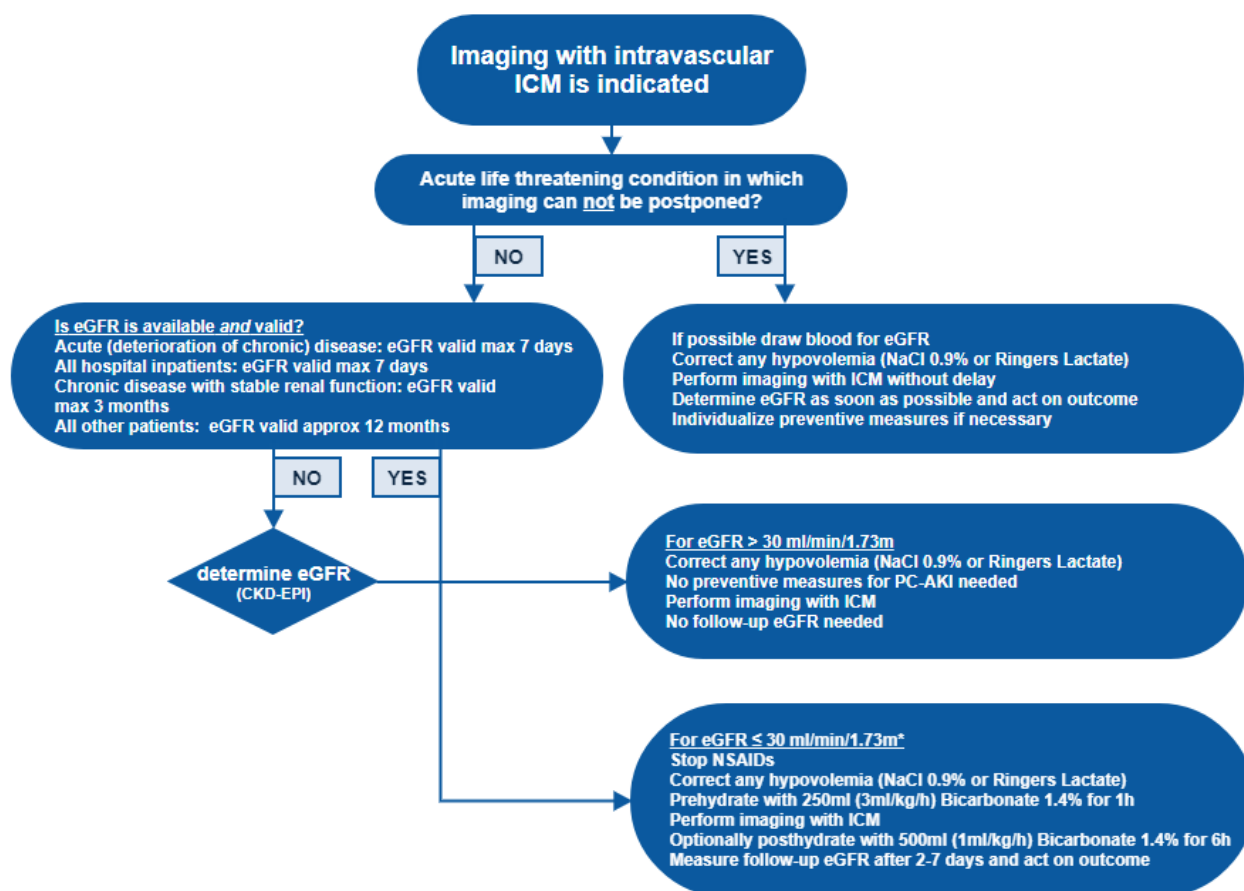
Use of iodine-containing contrast media in patients with type 2 diabetes and metformin use

Patients with type 2 diabetes often use metformin. Metformin lowers the glucose level in the blood. Patients with normal or mildly reduced renal function can continue to use metformin normally prior to and after an examination with iodine-containing contrast medium. However, in people with severe renal function loss there is a theoretical risk of a severe complication in which lactic acid accumulates leading to acidosis of the body (lactic acidosis).

I use metformin and have a renal disease. When should I stop metformin?

When in hospital an examination with iodine-containing contrast medium is scheduled, your renal function will be checked and your physician will evaluate if you have an increased risk of lactic acidosis. Patients using metformin that have a severe renal impairment (eGFR < 30 ml/min/1.73m²) and are scheduled for an examination with intravascular administration of iodine-containing contrast media are at increased risk. You will be asked to stop the metformin prior to the examination and your physician will check with a nephrologist and the doctor that has prescribed the metformin if you can continue with metformin after the examination. In case you have stop, your physician should prescribe a different anti-diabetic medication for you.

Flowchart



* For eGFR ≤ 15 ml/min/1.73m² or congestive heart failure NYHA 3-4

Stop NSAIDs. Consider alternative imaging without ICM. Correct any hypovolemia (NaCl 0.9% or Ringers Lactate). Individualize preventive hydration (by nephrologist/cardiologist). Perform imaging with ICM. Measure follow-up eGFR after 2-7 days and act on outcome.

Disclaimer

General

The aim of clinical guidelines is to help clinicians to make informed decisions about their patients. However, adherence to a guideline does not guarantee a successful outcome. Ultimately, healthcare professionals must make their own treatment decisions about care on a case-by-case basis, after consultation with their patients, using their clinical judgement, knowledge and expertise. A guideline is not intended to take the place of physician judgment in diagnosing and treatment of particular patients.

Guidelines may not be complete or accurate. The Working Group of this guideline and members of their boards, officers and employees disclaim all liability for the accuracy or completeness of a guideline, and disclaim all warranties, express or implied to their incorrect use.

Guidelines users always are urged to seek out newer information that might impact the diagnostic and treatment recommendations contained within a guideline.

Individualisation

In specific high risk patient groups (e.g. in patients with high-grade congestive heart failure or end-stage chronic kidney disease) clinicians may have to regress from these general guidelines and decide on individualisation of preventive measures to best fit the needs of their patients.

Life-threatening situations or conditions

In acute life-threatening situations or conditions clinicians may have to regress from these general guidelines and decide on individualisation of renal function estimation or preventive measures to best fit the needs of their patients in these situations or conditions.