Veilig gebruik van contrastmiddelen

Deze richtlijn is tot stand gekomen op initiatief van Nederlandse Vereniging voor Radiologie
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Waar gaat deze richtlijn over?

Deze richtlijn beschrijft hoe er bij patiënten, die voor beeldvormend onderzoek jodiumhoudend contrastmiddel krijgen toegediend, post-contrast acute nierschade (PC-AKI) kan worden voorkomen. In de richtlijn wordt in eerste instantie aandacht besteed aan indicatiestelling: welke patiënten hebben een verhoogd risico op PC-AKI en komen daarom in aanmerking voor preventieve maatregelen. Daarnaast wordt er aandacht besteed aan verschillende maatregelen die gebruikt kunnen worden om PC-AKI te voorkomen. De nadruk ligt hierbij op intraveneuze hydratie. Tot slot wordt er aandacht besteed aan de preventie van lactaatacidose my diabetes mellitus type 2 patiënten die metformine gebruiken.

Voor wie is deze richtlijn bedoeld?

Deze richtlijn is bedoeld voor alle artsen, die werkzaam zijn in het ziekenhuis en die beeldvormend onderzoek, al dan niet met een interventie, met contrastmiddel aanvragen of uitvoeren.

Voor patiënten

Deze richtlijn beschrijft de zorg voor patiënten die een beeldvormend onderzoek krijgen, waarbij contrastmiddel wordt toegediend. De richtlijn is bedoeld voor volwassen (>18 jaar) patiënten. Het gaat om jodiumhoudende contrastmiddelen die via een infuus worden ingespoten in de bloedvaten voor röntgenonderzoek, vaatonderzoek of vaatbehandeling.
Wanneer contrastmiddel in de bloedvaten komt, zou dit bij een kleine groep patiënten kunnen leiden tot nierschade. Deze nierschade wordt ook wel post-contrast acute nierschade (PC-AKI) genoemd. Deze schade zou voor een deel kunnen worden voorkomen door patiënten extra vocht toe te dienen via een infuus.
In deze richtlijn wordt eerst beschreven welke patiënten een verhoogd risico hebben op PC-AKI, en daarom in aanmerking komen voor preventieve maatregelen. Daarna wordt er ook beschreven welke preventieve maatregelen het beste genomen kunnen worden, om de kans op PC-AKI effectief te verkleinen. Tot slot wordt er nog extra aandacht besteed aan patiënten met diabetes type 2, die metformine gebruiken. Voor deze groep mensen gelden nog een aantal aanvullende maatregelen om melkzuurvergiftiging (lactaatacidose) te voorkomen.

Zie ook de patiëntensamenvatting (klik) bij deze richtlijn.

Hoe is de richtlijn tot stand gekomen?

De Nederlandse Vereniging voor Radiologie heeft een nieuwe set richtlijnen op het gebied van veiligheid van contrastmiddelen geprioriteerd als een belangrijk onderwerp van kwaliteitsbeleid. Reden hiertoe is dat er recentelijk veel onderzoeken zijn gepubliceerd op het gebied van veiligheid van het toedienen van contrastmiddelen. De richtlijn Voorzorgsmaatregelen bij Jodiumhoudende Contrastmiddelen uit 2007 was om deze reden niet meer actueel, en diende herzien of vervangen te worden door nieuwe richtlijnen. Het streven is om drie richtlijnen te publiceren over dit onderwerp, waarvan dit het eerste deel is.

Verantwoording

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Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Risk Stratification and Risk Stratification Tools

Uitgangsvraag

Hoe kunnen patiënten met een hoog risico op post-contrast acute nierschade (PC-AKI) bij toediening van intravasculair jodiumhoudend contrastmedium (CM) worden geïdentificeerd?

Subvragen

1. Wat is het risico op PC-AKI bij patiënten die jodiumhoudend contrast toegediend krijgen, vergeleken bij patienten die geen contrast krijgen toegediend?
2. Welke risicofactoren voor PC-AKI kunnen worden geïdentificeerd bij patiënten die een beeldvormend onderzoek met jodiumhoudend contrast ondergaan?
3. Hoe dient er rekening te worden gehouden met een niertransplantatie bij het inschatten van het risico op PC-AKI?
4. Hoe dient er rekening te worden gehouden met een solitaire nier bij het inschatten van het risico op PC-AKI?
5. Hoe dient er rekening te worden gehouden met de osmolaliteit van het jodiumhoudend contrastmiddel bij het inschatten van het risico op PC-AKI?
6. Wat is de rol van vragenlijsten en voorspellingsmodellen bij het inschatten van het risico op PC-AKI?

Aanbeveling

Voor patiënten die intravasculaire jodiumhoudend CM toediening ondergaan:
Beschouw patiënten met een eGFR <30 ml/min/1,73m^2 behorende tot een hoog-risico groep voor PC-AKI.

Consulteer een internist/nefroloog voor patiënten met een eGFR <30 ml/min/1,73m^2.

Pas dezelfde aanbevelingen toe bij patiënten met een niertransplantatie of een mononier als bij patiënten met bilaterale nieren die jodiumhoudend contrastmiddel krijgen toegediend.

Beschouw het risico van PC-AKI vergelijkbaar bij laag-osmolaire jodiumhoudend CM en iso-osmolaire jodiumhoudend CM wanneer deze intravasculair worden geïnjecteerd.

Optimale nefrologische zorg dient het primaire doel te zijn bij alle patiënten met chronische nierziekten, met specifieke aandacht voor hydratietoestand en medicatiegebruik.

Overweeg alternatieve beeldvorming zonder jodiumhoudend CM bij alle patiënten met een verhoogd risico op PC-AKI.

Streef naar klinische euvolemie voorafgaand aan een onderzoek met intravasculair jodiumhoudend CM.

Gebruik geen vragenlijsten en predictiemodellen om het risico van PC-AKI te schatten, omdat de validiteit en het effect hiervan op de klinische uitkomst onduidelijk is.

Overwegingen

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.

2 to 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/1.73m^2 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/1.73m^2, 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/1.73m^2. 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/1.73m^2 to 14% in the group with eGFR <30 ml/min/1.73m^2. 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/1.73m^2) 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.

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 both 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.

<u>Patients with a kidney transplantation and risk of PC-AKI</u>
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/1.73m^2 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 1 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/1.73m^2, for which hydration might be needed to prevent PC-AKI. Intravenous CM does not appear to be a risk factor in patients with stable eGFR between 30 and 60 ml/min/1.73m^2.

When iodine-containing CM is administrated intra-arterially, it is most likely an independent risk factor for PC-AKI in patients with stable eGFR of less than 30 ml/min/1.73m^2, 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 mgI) which is equivalent to CM volume x CM concentration. Typical values range from 30,000-60,000 mgI, 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 1 provides a help for conversion of iodine dose (in mg Iodine) to CM volume (in ml) and vice versa.

Table 1 Conversion of CM dose (in mgI) to CM volume (in ml) for CM concentrations @ 120 kVp

CM Dose in mgI	CM concentration in mgI/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

Inleiding

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 >44µmol/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/1.73m^2 to a nephrologist.

Conclusies

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. *(Bruce, 2009; McDonald, 2013)*

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 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 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.

Very low GRADE	We are uncertain what risk is of PC-AKI after iodinated CM in patients with a solitary kidney.

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)*

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)*

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)*

	No studies have been found that study prediction tools for PC-AKI risk in patients undergoing intra-venous iodine-containing contrast administration.

Samenvatting literatuur

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/1.73m^2 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/1.73m^2. IV LOCM did not appear to be associated with PC-AKI in patients with an eGFR >45 ml/min/1.73m^2.

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; Sonhaye, 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. (Aguiar-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; Lucrezziotti, 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 1, 2 and 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 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 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, 5 and 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 kg/m^2, risk factor in 2 out of 3 studies) or underweight (<18.5 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).

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/1.73m^2) 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 ≥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/1.73m^2). Seven patients developed PC-AKI (5.6%). Patients who developed PC-AKI had a mean age of 47 years, mean eGFR 78 ml/min/1.73m^2, 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/1.73m^2, 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. They included 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/1.73m^2 (33-90 ml/min/1.73m^2). 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 peri-procedural 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).

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/1.73m^2, 49% an eGFR 30-59 ml/min/1.73m^2, and 0.4% an eGFR <30 ml/min/1.73m^2. 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. How should the osmolality of iodine-containing contrast medium be taken into account when assessing PC-AKI risk?

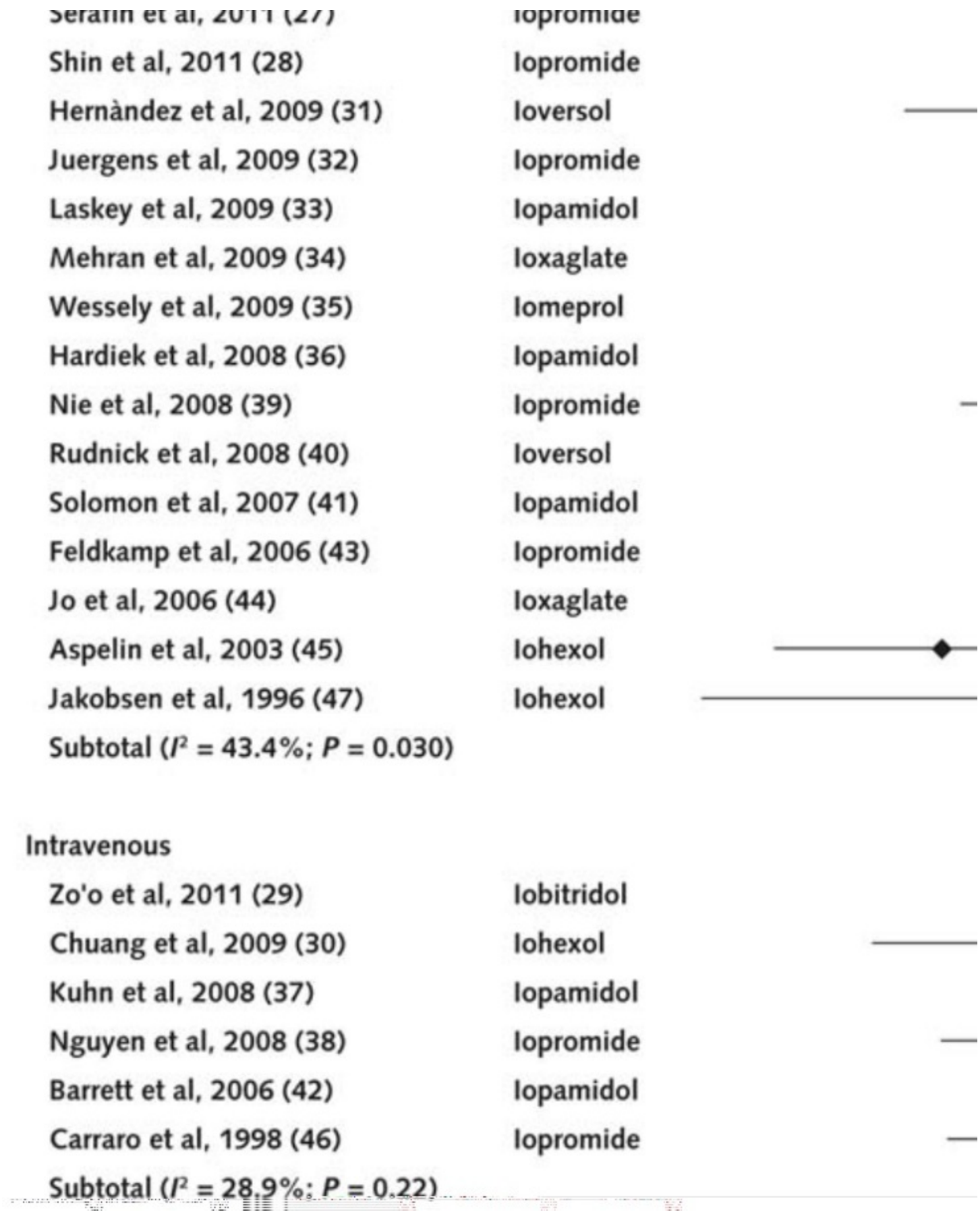
Description of studies

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 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 1 Pooled analysis of studies comparing different types of iodine-containing contrast medium. Reference for figure: Eng, 2016


Serafin et al, 2011 (27) Iopromide
Shin et al, 2011 (28) Iopromide
Hernàndez et al, 2009 (31) Ioversol
Juergens et al, 2009 (32) Iopromide
Laskey et al, 2009 (33) Iopamidol
Mehran et al, 2009 (34) Ioxaglate
Wessely et al, 2009 (35) Iomeprol
Hardiek et al, 2008 (36) Iopamidol
Nie et al, 2008 (39) Iopromide
Rudnick et al, 2008 (40) Ioversol
Solomon et al, 2007 (41) Iopamidol
Feldkamp et al, 2006 (43) Iopromide
Jo et al, 2006 (44) Ioxaglate
Aspelin et al, 2003 (45) Iohexol
Jakobsen et al, 1996 (47) Iohexol
Subtotal (I^2 = 43.4%; P = 0.030)
Intravenous
Zo'o et al, 2011 (29) Iobitridol
Chuang et al, 2009 (30) Iohexol
Kuhn et al, 2008 (37) Iopamidol
Nguyen et al, 2008 (38) Iopromide
Barrett et al, 2006 (42) Iopamidol
Carraro et al, 1998 (46) Iopromide
Subtotal (I^2 = 28.9%; P = 0.22)

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 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 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

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.

2 to 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 media 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.

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.

Zoeken en selecteren

To answer our clinical question a systematic literature analysis was performed for the sub questions 1-5. 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 1 – 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 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 was regarding patients with a history of kidney transplantation and one regarding 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.

Verantwoording

Laatst beoordeeld : 01-11-2017
Laatst geautoriseerd : 01-11-2017

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Evaluation of estimated glomerular filtration rate (eGFR)

Uitgangsvraag

Hoe dient nierfunctie te worden gemeten voor en na jodiumhoudend contrastmiddel toediening?

Subvragen

1. Wat is de beste manier om nierfunctie te meten?
2. Wanneer dient een eGFR schatting te worden uitgevoerd vooraf aan toediening van jodiumhoudend contrast?
3. Wanneer dient een eGFR schatting te worden uitgevoerd na toediening van jodiumhoudend contrast?
4. Indien PC-AKI wordt gediagnosticeerd, hoe dient de patiënt vervolgd te worden?
5. Hoe lang blijft een eGFR schatting geldig?

Aanbeveling

Aanbevelingen voor aanvragers van laboratoriumonderzoek
Bepaal de eGFR bij elke patiënt die een CT-scan of angiografie met of zonder interventie en gebruik van intravasculair jodiumhoudend contrastmiddel ondergaat, voorafgaand aan dit aanvullend onderzoek.

De eGFR meting is geldig gedurende:

- maximaal 7 dagen: wanneer de patiënt een acute ziekte of een verergering van een chronische ziekte heeft;
- maximaal 3 maanden: wanneer de patiënt een chronische ziekte heeft met een stabiele nierfunctie;
- circa 12 maanden bij alle andere patiënten.

Bepaal de eGFR binnen 2 tot 7 dagen na intravasculaire jodiumhoudende contrastmiddel toediening bij elke patiënt bij wie voorzorgsmaatregelen tegen PC-AKI zijn genomen.

Indien er PC-AKI wordt gediagnostiseerd (volgens Kidney Disease Improving Global Outcomes criteria), vervolg de patiënt gedurende minstens 30 dagen na de diagnose en bepaal het serum-kreatinine.

Aanbevelingen voor klinisch chemici
Meet het plasma-kreatinine middels een selectieve (enzymatische) methode.

Gebruik de kreatinine-gebaseerde Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formule voor de schatting van de eGFR.

Overweeg om de eGFR berekend met de CKD-EPI-formule te corrigeren voor het lichaamsoppervlak, indien beschikbaar.

Overwegingen

Formulas
MDRD equation (Levey, 2006)
eGFR (mL/min/1.73 m^2) = 175 × (Cr / 88.4)$^{-1.154}$ × age$^{-0.203}$ × 0.742 (if female)
× 1.210 (if African American)

CKD-EPI equation (Levey, 2009)
eGFR (mL/min/1.73 m^2) =
Female Cr ≤ 62 µmol/l: 144 x (Cr / 62)$^{-0.329}$ x 0.993^{Age}
Female Cr > 62 µmol/l: 144 x (Cr / 62)$^{-1.209}$ x 0.993^{Age}
Male Cr ≤ 80 µmol/l: 141 x (Cr / 80)$^{-0.411}$ x 0.993^{Age}
Male Cr > 80 µmol/l: 141 x (Cr / 80)$^{-1.209}$ x 0.993^{Age}
x 1.159 (if African American).

Note that Cr denotes creatinine concentration in both plasma and serum in µmol/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

Inleiding

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: Urinary volume * ($[creatinine]_{urine}$ /$[creatinine]_{plasma}$). 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; Schäffner, 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 * √(2)* √(√(CVa) + √(CVw))) when the two consecutive measurements of creatinine differ by at least 14,9%, e.g. when a value of 100 µmol/L increases to at least 115 µmol/L or a value of 150 µmol/L increases to at least 173 µmol/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-Malmo 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/1.73m^2.

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/1,73m^2 or ≥60 ml/min/1,73m^2. 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/1.73m^2.

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 descend, 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/1.73m^2 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).

Samenvatting literatuur

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

Verantwoording

Laatst beoordeeld : 01-11-2017
Laatst geautoriseerd : 01-11-2017

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Prevention of PC-AKI

This module consists of six submodules.

Verantwoording

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Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Prevention: Hydration and Complications

Uitgangsvraag

Welke hydratiestrategie dient te worden toegepast bij patiënten die intravasculair jodiumhoudendcontrastmiddel toediening ondergaan en een hoog PC-AKI risico hebben?

Aanbeveling

Voor patiënten met eGFR <30 ml/min/1,73m^2 die intravasculair jodiumhoudend CM toediening ondergaan kan één van de volgende opties worden toegepast:

1. Pas prehydratie toe met NaHCO3 1,4%, 3ml/kg/uur gedurende 1 uur vooraf aan CM toediening.
2. Pas pre- en posthydratie toe met NaHCO3 1,4%, 3ml/kg/uur (of 250 mL in totaal) gedurende 1 uur vooraf aan CM toediening en 1ml/kg/h (of 500mL in totaal) gedurende 6 uur na CM toediening.

Pas geen hydratie met gecontroleerde diurese toe ter preventie van PC-AKI bij patiënten die (cardiale) angiografie met of zonder interventie ondergaan, tenzij in studieverband.

Pas geen orale hydratie toe als enige preventie van PC-AKI.

Overwegingen

All studies
The number of patients with eGFR <30 ml/min/1.73m^2 is absent or very low in all described studies. No RCT has been publshed focusing on patients with eGFR <30 ml/min/1.73m^2 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/1.73m^2, shows that the incidence of PC-AKI is het 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/1.73m^2 or eGFR 45-59 ml/min/1.73m^2; 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 encouragment 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 $NaHCO_3$ 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 $NaHCO_3$ will raise the proximal tubular bicarbonate anion and pH levels close to those found in blood. Maintainance of $NaHCO_3$ 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 $NaHCO_3$ 1.4% for 1h pre-CM administration (Kooiman, 2014).

The landmark paper giving the first evidence on the effectiveness of $NaHCO_3$ pre- and post hydration was published in 2004 (Merten, 2004). This group describes an RCT consisting of 119 patients with a sCr ≥ 97,2 µmol/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 $NaHCO_3$ 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 ≥25% within 2 days after CM administration. The incidence of PC-AKI in the $NaHCO_3$ group was 1.7% (1 of 60) and 13.6% (8 of 59) in the NaCl group.

The positive results of this relatively short $NaHCO_3$ hydration schedule triggered a boom in RCTs comparing $NaHCO_3$ vs. NaCl. The mixture used in the landmark paper is not commercially available. The most resembling commercially available concentrations are $NaHCO_3$ 1.4% (i.e. 166 mEq/L $NaHCO_3$) 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 heterogenous 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 it somewhat lower osmolality and the reduced chance of hyperchloremic 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 a low dose diuretic, 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.

Inleiding

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.

Conclusies

Low GRADE	There is a low level of evidence that withholding hydration is as effective as single bolus hydration of 250ml $NaHCO_3$ in the prevention of PC-AKI prior to computed tomography pulmonary angiography with intravenous iodine-containing CM administration for suspected pulmonary embolism. *(Kooiman, 2014)*

Moderate GRADE	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/1.73m^2. *(Nijssen, 2017)*

Low GRADE	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. *(Cho, 2010)*

	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.

Low GRADE	Bicarbonate and saline pre- and post-hydration are similar in the prevention of PC-AKI independent on the administered schedules. *(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)*

Moderate GRADE	There is a moderate level of evidence that administration of 250ml $NaHCO_3$ 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. *(Kooiman, 2014)*

Low GRADE	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. *(Barbanti, 2015; Brar, 2014; Briguori, 2011; Marenzi, 2012; Qian, 2016; Usmiani, 2016; Visconti 2016)*

	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 contrast medium administration.

Samenvatting literatuur

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/1.73m^2, 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 form the analysis. Thus only two studies were included in the literature analysis.

Kooiman, 2014 described 138 patients with eGFR <60 ml/min/1.73m^2 undergoing chest CT for suspected pulmonary embolism. Sixty-seven patients received no hydration and the remaining 71 patients received 250ml $NaHCO_3$ 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/1.73m^2 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 post-contrast) (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 $NaHCO_3$, 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 condidered suitable for inclusion in the literature summary.

Cho, 2010 the RCT using both pre- and post hydration consisted of 91 patients with sCr >97,2 µmol/l or eGFR <60 ml/min/1.73m^2 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. $NaHCO_3$ 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 $NaHCO_3$ pre CM and 1.95g oral $NaHCO_3$ 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 heterogeniety 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 $NaHCO_3$ 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 $NaHCO_3$ 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 $NaHCO_3$ to saline hydration or exchanging saline by $NaHCO_3$ hydration for multiple hours;
4. One RCT compared in a non-inferiority trial, a 1-hour schedule of 250ml $NaHCO_3$ 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 $NaHCO_3$ (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, I2=60%, as shown in Figure 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 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 oedema) are shown in Table 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 toe heterogeniety 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 $NaHCO_3$ 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 $NaHCO_3$ (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/1.73m^2, in one paper <30 ml/min/1.73m^2 (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 recieved 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 recieved 1000 mL isotonic saline i.v. administration 12 h before procedure (rate-adjusted according to LVEF: 20– 40mL/h if LVEF<30%, 80–120 mL/h if LVEF 30–50%, 200 mL/h if LVEF >50%), plus 3 mL/kg/h 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 1mL/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 Briguori, 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/1.73m^2 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/1.73m^2 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/1.73m^2. After 1 month, mortality was similar in the intervention (6/146) and control (6/146) group, p=0.99; 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 RenalGuard group (p=0.005, odds ratio [OR] 0.076, 95% confidence interval [CI]: 0.009-0.66).

Brar, 2014 described that PC-AKI occured 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 occured 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 edema 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 heterogeniety of included studies.

Figure 1 Pooled analysis of PC-AKI risk in patients receiving short schedules of hydration with either bicarbonate or saline for CAG/PCI

Study or Subgroup	Bicarbonate - ss Events	Total	Saline - ss Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Adolph 2008	4	71	3	74	8.0%	1.39 [0.32, 5.99]
Boucek 2013	7	51	5	49	11.0%	1.35 [0.46, 3.96]
Brar 2008	21	175	24	178	16.3%	0.89 [0.51, 1.54]
Gomes 2012	9	150	9	151	12.7%	1.01 [0.41, 2.47]
Masuda 2007	2	30	10	29	8.2%	0.19 [0.05, 0.81]
Merten 2004	1	60	8	59	5.1%	0.12 [0.02, 0.95]
Ozcan 2007	12	88	4	88	10.8%	3.00 [1.01, 8.94]
Ratcliffe 2009	3	42	2	36	6.5%	1.29 [0.23, 7.27]
Recio - Mayorzal 2007	1	56	12	55	5.3%	0.08 [0.01, 0.61]
Solomon 2015	26	180	18	188	16.1%	1.51 [0.86, 2.65]
Total (95% CI)		**903**		**907**	**100.0%**	**0.88 [0.51, 1.50]**
Total events	86		95			

Heterogeneity: Tau² = 0.39; Chi² = 22.40, df = 9 (P = 0.008); I² = 60%
Test for overall effect: Z = 0.48 (P = 0.63)

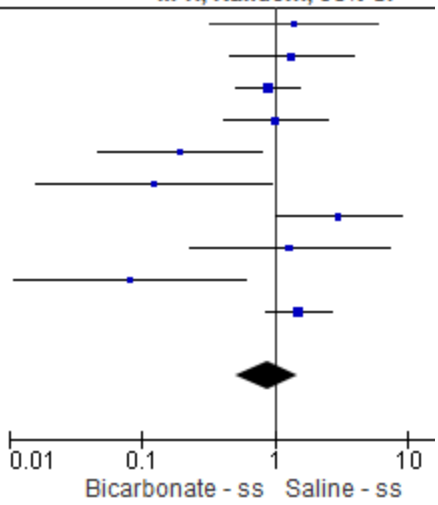

Figure 2 Pooled analysis of PC-AKI risk in patients receiving short schedules for bicarbonate versus long schedule for saline for CAG/PCI.

Study or Subgroup	Bicarbonate - ss Events	Total	Saline - ls Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Briguori 2007	2	111	11	198	6.1%	0.32 [0.07, 1.44]
Castini 2010	7	52	7	51	10.8%	0.98 [0.37, 2.60]
Hafiz 2012	14	159	19	161	15.9%	0.75 [0.39, 1.44]
Klima 2012	16	169	1	89	3.7%	8.43 [1.14, 62.50]
Koc 2013	15	94	6	101	11.7%	2.69 [1.09, 6.63]
Lee 2011	17	188	10	187	14.1%	1.69 [0.80, 3.60]
Maioli 2008	25	250	29	252	18.9%	0.87 [0.52, 1.44]
Nieto-Rios 2014	12	107	7	113	11.9%	1.81 [0.74, 4.43]
Shavit 2009	5	51	3	36	6.9%	1.18 [0.30, 4.61]
Total (95% CI)		**1181**		**1188**	**100.0%**	**1.23 [0.81, 1.87]**
Total events	113		93			

Heterogeneity: Tau² = 0.17; Chi² = 15.04, df = 8 (P = 0.06); I² = 47%
Test for overall effect: Z = 0.98 (P = 0.33)

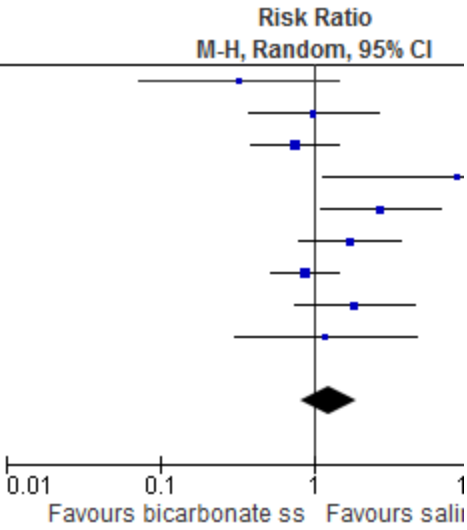

Table 1 Adverse events in bicarbonate versus saline infusion or controlled hydration versus standard hydration.

Author and date	Mortality		Dialysis		Heart failure or edema	
	Bicarbonate	Saline	Bicarbonate	Saline	Bicarbonate	Saline
Patients recieving 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 recieving 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 recieving 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
Totaal	11/532	29/539	3/566	21/586	10/221	14/218

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

Zoeken en selecteren

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 kideny 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 retrevied 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/1.73m^2
- 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 tekst 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.

Verantwoording

Laatst beoordeeld : 01-11-2017
Laatst geautoriseerd : 01-11-2017

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Use of Statins and hydration to reduce the incidence of PC-AKI in patients with pre-existent reduced kidney function receiving intravascular contrast medium

Uitgangsvraag

Dienen statines te worden aanbevolen naast hydratie om de kans om PC-AKI te verkleinen bij patiënten met chronische nierschade die intravasculair jodiumhoudend CM krijgen toegediend?

Aanbeveling

Overweeg het gebruik van een kortdurende (48 uur) hoge dosering atorvastatine of rosuvastatine naast hydratie in statine-naïeve patiënten met een eGFR <60 ml/min/1,73m^2 die coronair-angiografie ondergaan met of zonder coronaire interventie.

Overwegingen

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 <30ml/min/1.73m^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.

Inleiding

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.

Conclusies

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 coronary intervention. *(Liu, 2015)*

	The effects of statins on mortality start of dialysis and number of ICU admissions are uncertain in statin-naive 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.

Samenvatting literatuur

Description of studies

Risk of PC-AKI

Table 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/1.73m^2 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 (80 mg daily for 48 h) 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 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/secondar 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. Mortality: NI 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: NI Start dialysis NR ICU admission: NR
Han, 2014	30≤eGRF≤90 mL/min/1.73m^2. Here only the results of patients with eGRF≤60 mL/min/1.73m^2 were included. 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.	Increase in sCr concentration ≥0.5 mg/dl or ≥25% above baseline at 72h after exposure.	Rosuvastin 10 mg/day from 2 days before to 3 days after procedure.	Isotonic saline, 0.9% sodium chloride, 1mL/kg/h started 12h before and continued for 24h after the procedure.	PC-AKI: 3.6 Mortality: NR Start dialysis: NR ICU admission: NR	PC-AKI: 4.4 Mortality: NI Start dialysis NR ICU admission: NR

Leoncini, 2014	sCr ≤3mg/dL or without acute renal failure or renal replacement therapy. Here the results of a subgroup with eCrCL<60mL/min are presented. Statin-naïve patients with acute coronary syndrome undergoing early invasive strategy.	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.(Mortality: NI Start dialysis NR ICU admission: NR
Abaci, 2015	30≤eGRF≤60 mL/min/1.73m^2. Patients were naïve to statins and scheduled for elective coronary angiography	Increase in serum creatinine of ≥0.5 mg/dl or ≥25% from baseline <48 or 72 hours after angiography.	Rosuvastin 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: NI Start dialysis NR ICU admission: NR

Shehata, 2015	Diabetic patients, carrying the diagnosis of chronic stable angina and suffering from mild or moderate CKD. (eGFR 30– <90 mL/min/1.73 m	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 infusion of isotonic saline and oral N-acetylcysteine. Standard parenteral hydration protocol in both groups.	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: NI Start dialysis 0 ICU admission: NR
Qiao, 2015	1. Diabetic patients; 2. Mild to moderate CKD, which was defined as estimated glomerular filtration rate (eGFR) 30 to 89 ml/min per 1.73 m2; 3. Total CM administrated dose of volume ≥ 100 ml.	Relative increase in baseline SCr of ≥ 25% and/or an absolute increase of ≥ 0.5 mg/dl (44.2 µmol/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: NI 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.

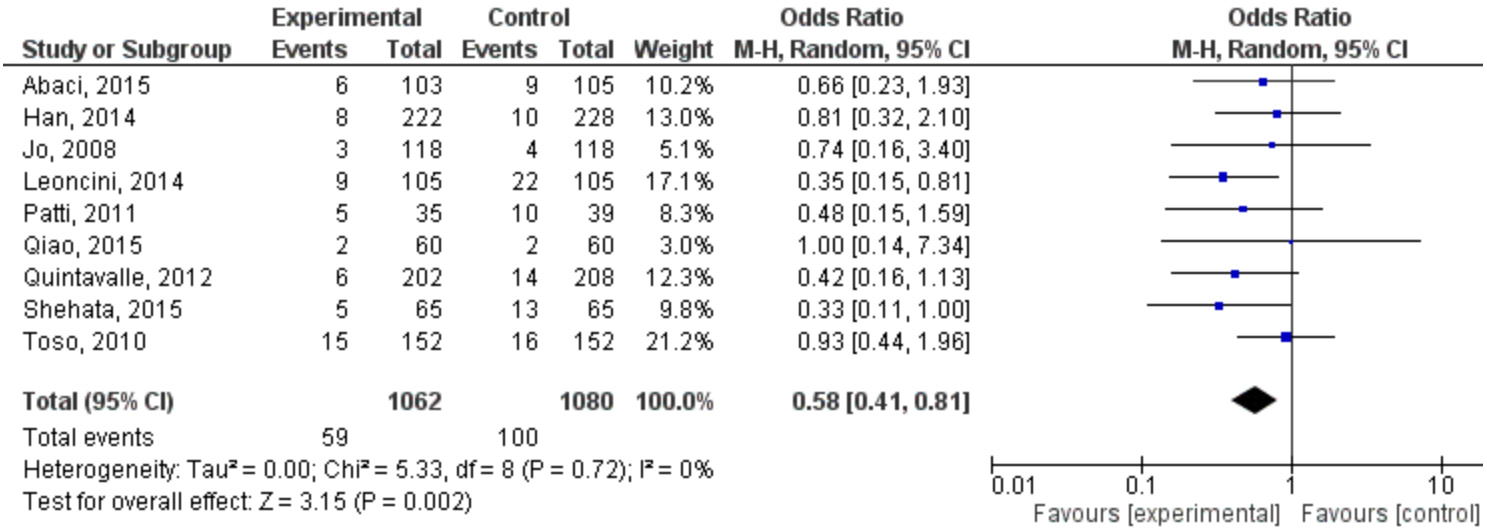
Abaci (2015) reported that 6 of the 103 patients in de rosuvastatin group and 9 of the 105 patients in the control group developed PC-AKI after the procedure.

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 1).

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



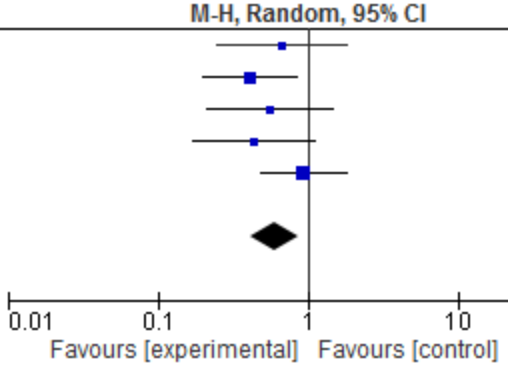
A separate meta-analysis (Figure 2) was performed to determine the effects of high dose rosuvastatin or atorvastatin on the risk of PC-AKI.

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 2 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

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Abaci, 2015	6	103	9	105	13.7%	0.68 [0.25, 1.84]
Leoncini, 2014	9	105	22	105	25.8%	0.41 [0.20, 0.85]
Patti, 2011	5	35	10	39	14.4%	0.56 [0.21, 1.47]
Quintavalle, 2012	6	202	14	208	15.5%	0.44 [0.17, 1.13]
Toso, 2010	15	152	16	152	30.6%	0.94 [0.48, 1.83]
Total (95% CI)		**597**		**609**	**100.0%**	**0.60 [0.41, 0.86]**
Total events	41		71			

Heterogeneity: Tau² = 0.00; Chi² = 3.28, df = 4 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.73 (P = 0.006)



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 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.

Zoeken en selecteren

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/1.73m^2;
- 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.

Verantwoording

Laatst beoordeeld : 01-11-2017
Laatst geautoriseerd : 01-11-2017

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

Abaci O, Arat Ozkan A, Kocas C, et al. Impact of Rosuvastatin on contrast-induced acute kidney injury in patients at high risk for nephropathy undergoing elective angiography. Am J Cardiol. 2015;115(7):867-71.
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Use of prophylactic N-acetylcysteine (NAC) in addition to hydration to reduce the incidence of PC-AKI in patients receiving intravascular iodine-containing contrast medium

Uitgangsvraag

Dient profylaxe met N-acetylcysteine (NAC) te worden aanbevolen naast hydratie om de kans om PC-AKI te verkleinen bij patiënten met een normale nierfunctie of met een chronische nierziekte die intravasculair CM krijgen toegediend?

Aanbeveling

Geef geen NAC ter preventie van PC-AKI aan patiënten met een normale of verminderde (eGFR <60 ml/min/1,73m^2) nierfunctie.

Overwegingen

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 (Submaramiam, 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 costs 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.

Inleiding

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 feed-back 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.

Conclusies

Low GRADE	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. *(Hsu, 2012)*

Low GRADE	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. *(Kama, 2014; 2006; Kitzler, 2012; Poletti, 2007; Poletti, 2013; Tepel, 2000)*

Low GRADE	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. *(Berwanger, 2013; Carbonell 2007; Jaffrey, 2015; Kim, 2010; Kinbara, 2010; Lawlor, 2007; Sadat, 2011; Sandhu, 2006; Tanaka, 2011; Thiele 2010)*

Low GRADE	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. *(ACT, 2011; Castini, 2010; Ferrario, 2009; Gulel, 2005; Habib, 2016, Izani Wan, 2008; Koc, 2012; Kotlyar, 2005; Sadenini, 2017; Seyon, 2007)*

	No studies were found that compared oral to intravenous N-acetylcysteine route of administration in patients undergoing intravascular iodine-containing contrast administration.

Samenvatting literatuur

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 1.

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 2.

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; Kotlyar, 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 3.

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 1 Meta-analysis of NAC vs Placebo in CT with intravenous CM administration in patients with eGFR <60 ml/min/1.73m^2.

Study or Subgroup	NAC plus hydration Events	Total	Placebo plus hydration Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kama 2014	7	36	5	35	28.3%	1.36 [0.48, 3.89]
Kitzler 2012	0	10	0	9		Not estimable
Poletti 2007	2	43	9	44	21.4%	0.23 [0.05, 0.99]
Poletti 2013	14	52	13	58	35.4%	1.20 [0.62, 2.31]
Tepel 2000	1	41	9	58	14.9%	0.16 [0.02, 1.19]
Total (95% CI)		**182**		**204**	**100.0%**	**0.64 [0.24, 1.70]**
Total events	24		36			

Heterogeneity: Tau² = 0.58; Chi² = 8.12, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 0.89 (P = 0.37)

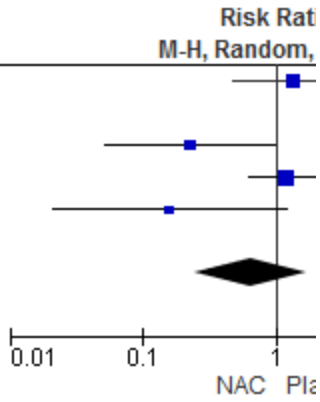


Figure 2 Meta-analysis of NAC vs Placebo in Coronary angiography with intra-arterial CM administration in patients with normal kidney function

Study or Subgroup	NAC plus hydration Events	Total	placebo plus hydration Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ACT 2011	122	889	122	905	41.3%	1.02 [0.81, 1.29]
Carbonell 2007	11	107	11	109	10.0%	1.02 [0.46, 2.25]
Jaffrey 2012	33	192	25	206	21.0%	1.42 [0.88, 2.29]
Kim 2010	3	80	7	86	4.0%	0.46 [0.12, 1.72]
Kinbara 2010	0	15	4	15	0.9%	0.11 [0.01, 1.90]
Lawlor 2007	3	46	3	48	3.0%	1.04 [0.22, 4.91]
Sadat 2011	1	21	3	19	1.6%	0.30 [0.03, 2.66]
Tanaka 2011	3	53	0	53	0.9%	7.00 [0.37, 132.29]
Thiele 2010	18	126	25	123	17.4%	0.70 [0.40, 1.22]
Total (95% CI)		**1529**		**1564**	**100.0%**	**0.97 [0.74, 1.28]**
Total events	194		200			

Heterogeneity: Tau² = 0.03; Chi² = 10.09, df = 8 (P = 0.26); I² = 21%
Test for overall effect: Z = 0.22 (P = 0.82)

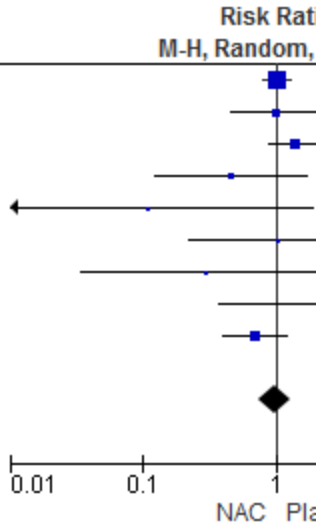
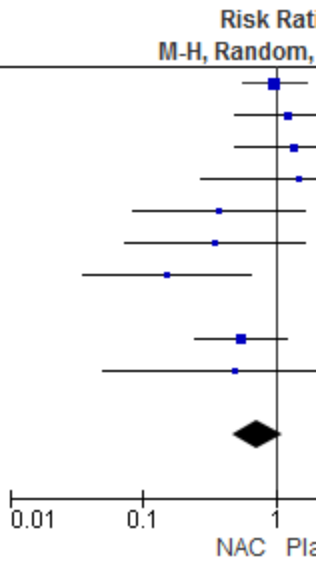


Figure 3 Meta-analysis of NAC vs Placebo in Coronary angiography with intra-arterial CM administration in patients with eGFR <60 ml/min/1.73m^2.

Study or Subgroup	NAC plus hydration Events	Total	placebo plus hydration Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ACT 2011	24	260	20	214	24.7%	0.99 [0.56, 1.74]
Castini 2011	9	53	7	51	14.9%	1.24 [0.50, 3.07]
Ferrario 2009	8	99	6	101	12.8%	1.36 [0.49, 3.78]
Gulel 2005	3	25	2	25	5.7%	1.50 [0.27, 8.22]
Habib 2016	2	30	8	45	7.3%	0.38 [0.09, 1.65]
Izan Wan 2008	2	49	6	51	6.7%	0.35 [0.07, 1.64]
Koc 2012	2	80	13	80	7.4%	0.15 [0.04, 0.66]
Kollyar 2005	0	41	0	19		Not estimable
Sadineni 2017	7	35	11	30	17.2%	0.55 [0.24, 1.23]
Seyon 2007	1	20	2	20	3.3%	0.50 [0.05, 5.08]
Total (95% CI)		**692**		**636**	**100.0%**	**0.73 [0.47, 1.13]**
Total events	58		75			

Heterogeneity: Tau² = 0.12; Chi² = 11.17, df = 8 (P = 0.19); I² = 28%
Test for overall effect: Z = 1.42 (P = 0.16)



Zoeken en selecteren

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 (congestion, intensive care unit admittance, and 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 ml/min1.73m^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, and mortality), and 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 (eGFR≥60 ml/min1.73m^2). The reason for this was that the working group decided to focus the recommendations on patients with an impaired eGFR (<60 ml/min1.73m^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 (eGFR≥60 ml/min1.73m^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 under the tab Onderbouwing.

Verantwoording

Laatst beoordeeld : 01-11-2017
Laatst geautoriseerd : 01-11-2017

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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

Uitgangsvraag

Dient profylaxe met Vitamine C te worden aanbevolen naast hydratie om de kans om PC-AKI te verkleinen bij patiënten met chronische nierziekte die intravasculair CM krijgen toegediend?

Aanbeveling

Geef Vitamine C niet exclusief ter preventie van PC-AKI bij patiënten met een normale of verminderde (eGFR <60 ml/min/1,73m^2) nierfunctie.

Overwegingen

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 m^2. 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.

Inleiding

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).

Conclusies

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. *(Komiyama, 2017; Dvoršak, 2013; Sadat, 2013)*

	No studies were found evaluating the effects of vitamin C administration on PC-AKI in patients undergoing CT scans with intravascular contrast administration.

Samenvatting literatuur

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 1. 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 1 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 mmol/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 mmol/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 mmol/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 an 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
Albabtain 2013	Saoudi Arabia	SCr >112 mmol/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 mmol/L	3 g before, 2 g night before and morning after	oral	50-100 ml/h for 2-h before and 6-h afer	5	7.3
Hamdi [a.b] 2013	Tunesia Abstract	All, Exclusion: cronic dialysis, AKI, heart failure, use of Vit C Baseline SCr 98.6 ± 29 mmol/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 m2)	3g before the procedure, 2g after and the next day in combination with 20 mEq (in 20 ml) sodium bicarbonate befor 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
[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 1), 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 1.

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 that includes the studies that appeared in abstract form as well (figure 2) and one that includes all RCTs on vitamin C (figure 3). Both demonstrate a similar effect as the meta-analysis in figure 1.

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 1 Meta-analysis of Vitamin C in patients undergoing coronary angiography

Study or Subgroup	vitamin C plus hydration Events	Total	hydration Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Albabtain 2013	2	57	5	66	4.7%	0.46 [0.09, 2.30]
Boscheri 2007	5	74	3	69	6.0%	1.55 [0.39, 6.26]
Brueck 2011	24	98	62	193	42.7%	0.76 [0.51, 1.14]
Dvorsak 2013	2	40	3	41	4.0%	0.68 [0.12, 3.88]
Komiyama 2017	6	211	19	218	13.4%	0.33 [0.13, 0.80]
Spargias 2004	11	118	23	113	21.6%	0.46 [0.23, 0.90]
Zhou 2011	6	82	4	74	7.7%	1.35 [0.40, 4.61]
Total (95% CI)		**680**		**774**	**100.0%**	**0.65 [0.45, 0.92]**
Total events	56		119			

Heterogeneity: Tau² = 0.03; Chi² = 6.99, df = 6 (P = 0.32); I² = 14%
Test for overall effect: Z = 2.41 (P = 0.02)

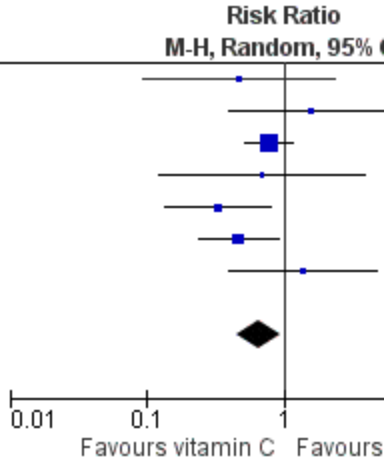

Figure 2 Meta-analysis also including the studies published in abstract form only

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

Figure 3 Meta-analysis including all RCTs on vitamin C (both impaired kidney function and kidney function not reported)

Study or Subgroup	ascorbic acid		placebo		Weight	Risk Ra
	Events	Total	Events	Total		M-H, Random
Spargias 2004	11	118	23	113	17.1%	0.46 [0.
Boscher 2007	5	74	3	69	4.4%	1.55 [0.
Zhou 2011	6	82	4	74	5.6%	1.35 [0.
Komiyama 2011	3	35	12	35	6.1%	0.25 [0.
Li 2012	5	78	4	71	5.2%	1.14 [0.
Albabtain 2013	2	57	5	66	3.4%	0.46 [0.
Dvorsak 2013	2	40	3	41	2.9%	0.68 [0.
Hamdi 2013	11	107	20	95	16.6%	0.49 [0.
Bruerck 2013	24	98	62	193	38.6%	0.76 [0.
Total (95% CI)		689		757	100.0%	0.65 [0.
Total events	69		136			
Heterogeneity: Tau² = 0.02; Chi² = 8.67, df = 8 (P = 0.37); I² = 8%						
Test for overall effect: Z = 2.88 (P = 0.004)						

Zoeken en selecteren

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 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, or 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 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, and mortality), and cost-effectiveness.

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.

Verantwoording

Laatst beoordeeld : 01-11-2017
Laatst geautoriseerd : 01-11-2017

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Discontinuation of nephrotoxic medication prior to intravascular contrast administration to reduce the risk of post-contrast acute kidney injury (PC-AKI)

Uitgangsvraag

Dient nefrotoxische medicatie te worden gestaakt vooraf aan intravasculaire jodiumhoudend contrastmiddel toediening om het risico van PC-AKI te verkleinen?

Aanbeveling

Staak ACE-remmers, angiotensine II receptorantagonisten of diuretica niet routinematig vooraf aan intravasculaire jodiumhoudend contrastmiddel toediening.

Staak NSAID's vooraf aan toediening van intravasculair jodiumhoudend contrastmiddel.

De werkgroep beveelt een nefrologisch consult aan, vooraf aan jodiumhoudend CM toediening, bij patiënten met een eGFR <30 ml/kg/1,73m^2, zodat er op individuele basis kan worden besloten om ACE-remmers, angiotensine II receptorantagonisten, diuretica of nefrotoxische medicatie te continueren of te staken, en de potentiële voor- en nadelen van jodiumhoudend CM-toediening tegen elkaar af te wegen.

Overwegingen

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, post-glomerular vasoconstriction increases filtration pressure. Thus, if glomerular filtration depends on post-glomerular 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 post-glomerular 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 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 post-glomerular 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 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 nephrological consultation before administering iodine-containing CM in patients with eGFR <30 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 nephrological consultation before administering iodine-containing CM in patients with eGFR <30 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 nephrological consultation before administering iodine-containing CM in patients with eGFR <30 ml/kg/1.73m^2 crucial to individualize continuation or discontinuation of these specific medications.

Inleiding

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?

Conclusies

Low GRADE	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. *(Rosenstock, 2008)*

Low GRADE	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. *(Bainey, 2015)*

Very Low GRADE	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. *(Bainey, 2015)*

	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.

Samenvatting literatuur

ACE inhibitors and Angiotensin-II Receptor Blockers

Description of studies
This literature summary describes 2 randomized controlled trials (RCTs) (Bainey, 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 whom 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/1.73m^2). 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.

Bainey, 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.

Bainey, 2015 included 208 patients with moderate renal insufficiency (≥ 150 µmol/l within 3 months or ≥ 132 µmol/l within one week of cardiac catheterisation). Use of Angiotensin II blockers were 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±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

Rosenstock, 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).

Bainey, 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 re-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 Bainey, 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.

Zoeken en selecteren

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 under the Tab “Verantwoording”. 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/1,73m^2 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.

Verantwoording

Laatst beoordeeld : 01-11-2017
Laatst geautoriseerd : 01-11-2017

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

Bainey KR, Rahim S, Etherington K, Et al. Effects of withdrawing vs continuing renin-angiotensin blockers on incidence of acute kidney injury in patients with renal insufficiency undergoing cardiac catheterization: Results from the Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker and Contrast Induced Nephropathy in Patients Receiving Cardiac Catheterization (CAPTAIN) trial. Am Heart J. 2015; Jul;170(1):110-6.
Rosenstock JL, Bruno R, Kim JK, et al. The effect of withdrawal of ACE inhibitors or angiotensin receptor blockers prior to coronary angiography on the incidence of contrast-induced nephropathy. Int Urol Nephrol. 2008;40(3):749-55.

Use of prophylactic renal replacement therapy to reduce the risk of PC-AKI in patients with CKD stage 4 to 5 receiving intravascular contrast medium

Uitgangsvraag

Dient profylactische nierfunctievervangende therapie te worden aanbevolen bij patiënten met chronisch nierfalen stadium 4-5, die intravasculaire jodiumhoudend contrastmiddel toegediend krijgen bij coronaire angiografie met of zonder percutane interventie, om het risico op PC-AKI te verminderen?

Subquestion
Should the dialysis schedule be adapted when a CKD stage-5 patient receives intravascular contrast medium?

Aanbeveling

Gebruik geen profylactische hemodialyse bij niet dialyse-afhankelijke patiënten met chronische nierschade stadium 4-5, die intravasculair jodiumhoudend contrastmiddel toegediend krijgen bij coronaire angiografie met of zonder percutane interventie, om het risico van PC-AKI te verminderen.

Gebruik profylactische hemofiltratie niet routinematig bij patiënten met chronische nierschade stadium 4-5, die intravasculair jodiumhoudend contrastmiddel toegediend krijgen bij coronaire angiografie met of zonder percutane interventie.

Pas het hemodialyseschema van patiënten met chronische nierfunctievervangende therapie niet aan, wanneer deze patiënten intravasculair jodiumhoudend contrastmiddel toegediend krijgen. (In andere woorden: bij het inplannen van een onderzoek met jodiumhoudend CM hoeft er geen rekening gehouden worden met het dialyse-schema van de patënt.)

Overwegingen

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/1.73m^2), (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.

Inleiding

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 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 that haemodialysis.

In patients with an eGFR <30 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 1). Thus in patients with CKD stage 4-5, hemofiltration significantly adds to the removal of the CM.

Figure 1 from Gastoni (1)

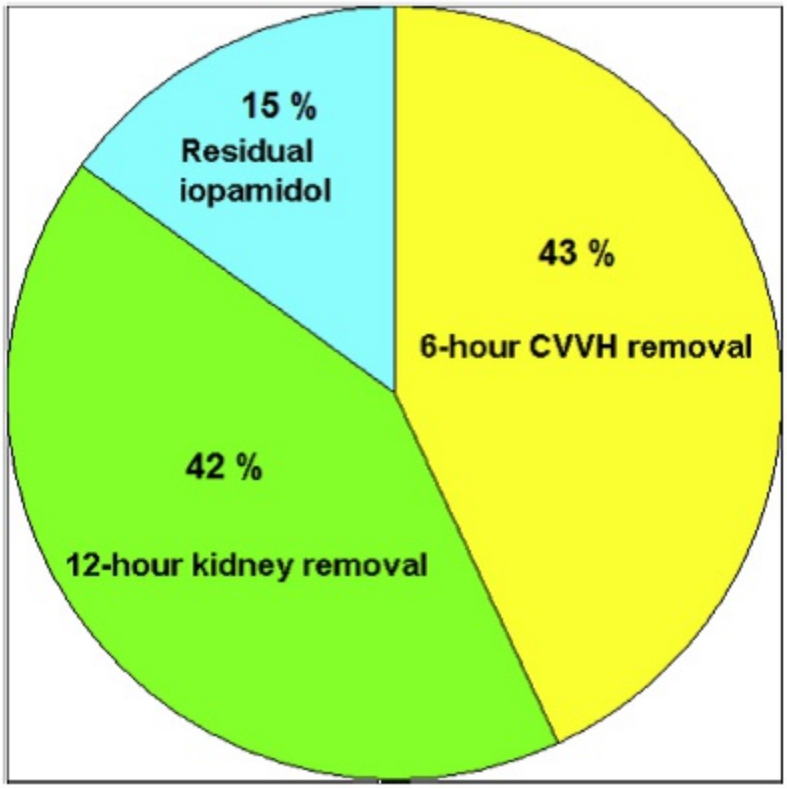


Figure 2. Iopamidol removal (expressed as percentage of total infused dose) by 6-hour CVVH and 12-hour diuresis. Residual iopamidol represents the difference between total infused iopamidol and total iopamidol removed by both kidney and CVVH.

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 (eGFR <30 ml/min/1.73m^2) receiving intravascular iodine-containing CM.

Conclusies

Very Low GRADE	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/1.73m^2) receiving intravascular iodine-containing contrast administration for coronary angiography with or without percutaneous intervention. *(Cruz, 2012)*

Very Low GRADE	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. *(Cruz, 2012)*

Very Low GRADE	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. *(Cruz, 2012)*

Very Low GRADE	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. *(Spini, 2013; Marenzi 2006)*

Samenvatting literatuur

Description of studies
One 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 radiocontrast 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 sub analysis. 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 venovenous hemofiltration (CVVH) for patients with serum creatinine <265 µmol/L or continuous venovenous hemodiafiltration (CVVHDF) for patients with serum creatinine >265 µmol/L, initiated 6 to 8 hours before PCI and restarted immediately after 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 1.

Table 1 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/1.73m^2, stage 4 15-30 ml/min/1.73m^2, stage 5 <15 ml/min/1.73m^2; 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 2). 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 2).

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 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 2.

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 3.

Figure 2 Pooled analysis of PC-AKI risk in CKD 4-5 patient undergoing CAG and/or PCI and receiving either HD or SMT

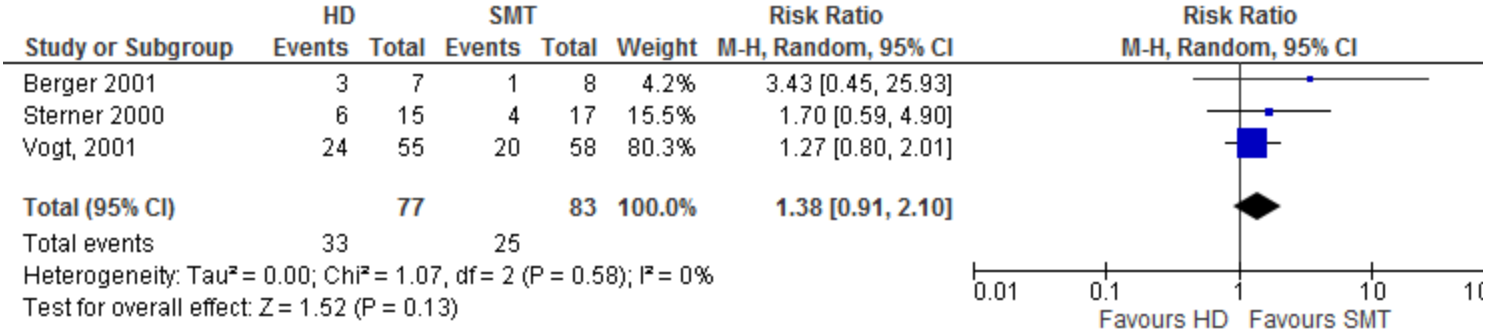
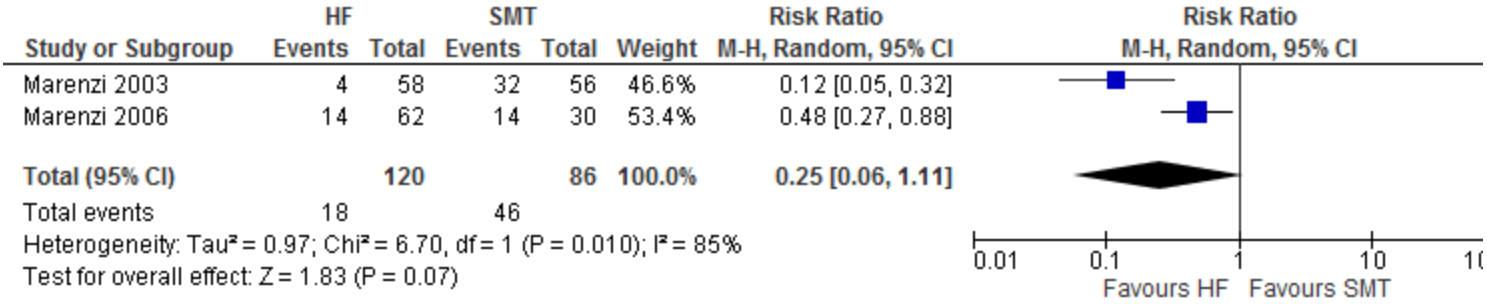


Figure 3 Pooled analysis of PC-AKI risk in CKD 4-5 patient undergoing CAG and/or PCI and receiving either HF or SMT



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).

Zoeken en selecteren

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/1.73m^2) receiving intravascular contrast?

P (patient category) patients with impaired kidney function (eGFR less than 30 ml/min/1.73m^2) 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/1.73m^2);
- 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, and mortality), and 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.

Verantwoording

Laatst beoordeeld : 01-11-2017
Laatst geautoriseerd : 01-11-2017

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Iodine-containing contrast medium use in type-2 diabetic patients using metformin

Uitgangsvraag

Dient metformine te worden gestaakt voorafgaand aan intravasculaire jodiumhoudend contrastmiddel toediening om metformine-geassocieerde lactaatacidose te voorkomen?

Aanbeveling

Continueer metformine bij elke patiënt met een eGFR ≥30 ml/min/1,73m^2 bij wie het jodiumhoudend contrastmiddel intravasculair wordt toegediend.

Staak metformine bij alle patiënten met een eGFR <30ml/min/1,73m^2 bij wie intravasculair jodiumhoudend contrastmiddel wordt toegediend zodra dit niveau van nierschade is gedetecteerd, en informeer de aanvrager van het onderzoek en voorschrijver van metformine.

Overwegingen

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 antihyperglycaemic 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. 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 m^2. 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/1.73m^2), 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/1.73m^2 and starting metformin in patients with an eGFR between 30 to 44 ml/min/1.73m^2 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 and 60 ml/min/1.73 m^2. 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 m^2 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 m^2 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 m^2. In agreement with the FDA guideline metformin is contraindicated in patients with an eGFR <30 ml/min/1.73 m^2.

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/1.73m^2 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 m^2.

Inleiding

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 administrated?
- 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?

Conclusies

	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. *(Georgen, 2010)*

Samenvatting literatuur

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.

Zoeken en selecteren

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/1,73m^2;
- 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

Verantwoording

Laatst beoordeeld : 01-11-2017
Laatst geautoriseerd : 01-11-2017

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Organization of Health Care PC-AKI

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 administrated 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	*Before procedure:* Administrate hydration Record hydration in patient record (type/name, concentration, volume, duration) ***After procedure:*** check eGFR If PC-AKI, then treatment and follow-up and record PC-AKI in patient record
Physician responsible for the procedure	*Before and during procedure:* 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/1.73m^2, 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. CO_2 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.

Verantwoording

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Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.