# Veilig gebruik van contrastmiddelen

Deze richtlijn is tot stand gekomen op initiatief van Nederlandse Vereniging voor Radiologie

# Inhoudsopgave

# Startpagina - Veilig gebruik van contrastmiddelen

**Reason for making this guideline**
The Radiological Society of the Netherlands (Nederlandse Vereniging voor Radiologie/NVvR) deemed a set of new guidelines on the Safe Use of Contrast Media (CM) highly necessary and relevant. In radiology, contrast media, such as Iodine-based Contrast Media (ICM) and Gadolinium Based Contrast Agents (GBCA), are extensively used. The overall goal of this set of guidelines was to increase safety and awareness around contrast media. Practical recommendations are given in each chapter.

The four parts of the Safe Use of Contrast Media guidelines cover the following topics regarding CM safety:

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

- Prevention of contrast-associated acute kidney injury (CA-AKI*) from iodine-based contrast media
- Iodine-based contrast media use in patients with type-2 diabetes taking metformin
- Iodine-based contrast media use in patients on chronic dialysis

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

- Prophylaxis and management of hypersensitivity reactions to contrast media
- Safe use of gadolinium-based contrast agents, in terms of prevention of post-contrast acute kidney injury (PC-AKI) and Nephrogenic systemic fibrosis (NSF)
- Contrast media injections with power injectors through (peripherally inserted) central venous lines and implantable ports
- Contrast media extravasation

Safe Use of Contrast Media - Part 3 (finalized in 2022):

- Prevention of iodine-induced hyperthyroidism
- Safe use of contrast media use during pregnancy and lactation
- Safe use of contrast media use in patients with rare diseases:
    - Patients with Multiple Myeloma (M. Kahler)
    - Patients with Pheochromocytoma and Paraganglioma
    - Patients with Myasthenia Gravis
    - Patients with Mastocytosis
- Safe time intervals between contrast-enhanced studies
- Prevention of recurrent hypersensitivity reactions to contrast media (update of part 2), including the Weber and Lalli effects
- Analytical Interference of contrast media with clinical laboratory tests
- Gadolinium deposition in the body after gadolinium-based contrast agents (both update of part 2 and a new module about strategies for GBCA dose reduction)

Safe Use of Contrast Media - Part 4 Children (finalized in 2024):
• Risk stratification in the Prevention of Post Contrast Acute Kidney Injury (PC-AKI)
• Hydration Strategies in the Prevention of PC-AKI

- Profylactic Measures for Hypersensitivity Reactions
- Treatment of Acute hypersensitivity reactions
- Monitoring of Thyroid Function after Administration of Iodine-based Contrast Media

*Note: Post-contrast acute kidney injury is synonymous with contrast-associated acute kidney injury Guideline Safe Use of Contrast Media part 4 Guideline for Authorisation phase June 2024.

**Aim of the current guideline**
The aim of the Safe Use of Contrast Media guidelines is to critically review the recent evidence and try to formulate new practical guidelines for all hospital physicians to provide the safe use of contrast media in diagnostic and interventional studies in children (younger than 18 years) and adults (18 years and older). The ultimate goal of this guideline is to increase the quality of care, by providing efficient and expedient healthcare to children that may benefit from this healthcare and simultaneously guard patients from ineffective care. Furthermore, such a guideline should ideally be able to save money and reduce day-hospital waiting lists.

**Focus of the guideline**
The Safe Use of Contrast Media guidelines focus on all child (younger than 18 years) and adult (18 years and older) patients that receive CM during radiologic or cardiologic studies or interventions. The patient population for which these guidelines are developed are patients who receive intravascular, oral or intracavitary (intra-articular, intra-vesical, intra-cholangiographic) contrast media both in the clinical setting, as well as for outpatients. The guidelines do not cover radiopharmaceuticals used in nuclear medicine.

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

**For children and their caretakers**
The modules for children under the age of 18 are specifically designed for a relatively vulnerable patient group. Besides the child who sometimes has to undergo additional blood collections and procedures, the parents/caretakers also need to be informed about and consent to the necessary measures.

Patients and parents/caretakers want to make decisions based on the available evidence and best clinical practice. This emphasizes the importance of comprehensive and understandable information and the management of patient and parent/caretaker anxiety that can arise when using this guideline.

Keeping patient and parents/caretakers informed in a calm atmosphere, will eventually reduce stress and anxiety.

**Terminology and definitions**
The terminology and definitions of specific topics will be discussed in each of the specific topics/modules of this guideline. Abbreviations used in this guideline can be found below.

## Guideline Disclaimers

General

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

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

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

Individualisation

In specific high-risk patient groups clinicians may have to regress from these general guidelines and decide on individualisation to best fit the needs of their patients.

Life-threatening situations or conditions

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

Documentation

The guideline development group recommends documenting the specific contrast medium name and dose which were administered to the patient (in the imaging report and/or with the stored images).

## Verantwoording

Laatst beoordeeld : 01-12-2024

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

# PC-AKI

This module consists of four submodules.

## Verantwoording

Laatst beoordeeld :

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

# Definities, terminologie en klinisch verloop

*Disclaimer: This narrative review has been written by members of the Guideline Development Group so that non-specialized readers can follow the Modules about Hypersensitivity more easily. It was not part of the actual guideline process with structured literature analyses.*

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

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

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

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

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

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

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

During the first meeting of the Acute Kidney Injury Network (AKIN), a network of experts in Critical Care and Nephrology, the term Acute Kidney Injury (AKI) was suggested as the preferred uniform terminology for acute renal failure. This was diagnosed as "an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine (sCr) of ≥ 0.3 mg/dl (≥ 26.4 µmol/l), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for more than six hours)" (Mehta, 2007). In clinical practice a 50% increase in sCr >3 and <7 days can be used. This definition is thus applicable to all forms of AKI and is not specific for contrast-induced AKI. This was subsequently adapted into the KDIGO Practice Guidelines in 2012. According to this guideline, AKI can be subdivided in 3 stages (see Table 1) according to criteria adapted from the RIFLE (Risk, Injury, Failure, Loss, End Stage) criteria (Drüeke, 2012):

**Table 1: KDIGO staging of AKI**

| *Stage* | *Serum creatinine criteria* | *Urine output criteria* |
|---|---|---|
| 1 | sCr increase ≥0.3 mg/dl (≥26.5 µmol/l), or<br>sCr increase ≥1.5 to 1.9x baseline | <0.5 ml/kg/h for 6 to 12h |
| 2 | sCr increase >2.0 to 2.9x baseline | <0.5 ml/kg/h for ≥12h |
| 3 | sCr ≥4.0 mg/dl (≥354 µmol/l)<br>sCr increase >3.0 x baseline or<br>initiation of renal replacement therapy | <0.3 ml/kg/h for ≥24h<br>Anuria for ≥12h |

**Of note 1 mg/dl serum Creatinine equals 88,4 µmol/l.**

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

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

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

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

Already in 2006, a CIN Consensus Working Panel formed by GE Healthcare with experts from various disciplines indicated that the ADQI-RIFLE criteria may be important in the future for defining PC-AKI (McCullough, 2006). Many researchers in radiology and cardiology are now moving towards adaptation of the AKIN criteria as the standard for studies on contrast-induced AKI (Garfinkle, 2015). Therefore, we suggest, similar to the European Renal Best Practice (ERBP) working group in their comment on the KDIGO 2012 practice guidelines on AKI, that there seems to be no good reason why the definition of PC-AKI (or CI-AKI) should be different from the general definition of other forms of AKI (Fliser, 2012; Kooiman, 2016; Thomas, 2015), even though CI-AKI /CIN and PC-AKI are not completely interchangeable.

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

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

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

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

Two recent meta-analyses of 40 and 42 studies in about 19,000 patients undergoing CE-CT revealed a weighted pooled incidence of PC-AKI of 6.4% (95%CI 5.0-8.1%) and 5.0% (95%CI 3.8-6.5%). (Kooiman, 2012; Moos, 2013) In the meta-analysis of Moos et al. chronic kidney disease (CKD), diabetes, malignancy, age >65 years and use of non-steroidal anti-inflammatory drugs (NSAID's) and in the meta-analysis of Kooiman et al. CKD and diabetes were associated with an increased risk. In about 1% of all patients (follow-up one week to two months after CE-CT) the renal function decline persisted, but the weighted pooled incidence of renal replacement therapy was as low as 0.06%. (Kooiman, 2012) The authors of this meta-analysis conclude that, given the low incidence of PC-AKI in general and the rare occurrence of a persistent decline in renal function, CM in the setting of a CT can be safely administered to the vast majority of patients. However, as emphasized by the authors, since in most of the studies pre- and post-hydration was performed in patients at high risk for PC-AKI, the results are not generalizable to high risk patients without pre- and/or post-hydration.

Meta-analyses of non-randomized studies comparing outcomes of patients who underwent CT with and without iodine-containing CM bear the risk of selection bias. Recently, propensity score matching has been introduced to the field of PC-AKI. Propensity score matching is a statistical method used in observational studies with low incidence of outcome under study that takes measured confounding into account (Rosenbaum, 1984). McDonald JS, et al. performed a propensity score-based matched study in over 12,500 patients, and did not find an increased risk of PC-AKI, acute dialysis, or 30-day mortality in patients who underwent CE-CT versus those who did not. (McDonald, 2014) Using propensity-score based matching in over 17,500 patients Davenport et al. also did not observe an increased risk for AKI in patients with normal renal function after intravenous CM administration for CT, but they reported an increased incidence of AKI in patients with an eGFR <30 ml/min/1.73m$^2$ (Davenport, 2013). These findings suggest that the incidence of CI-AKI in patients undergoing contrast-enhanced CT with intravenous iodine-containing CM administration is likely to be substantially lower than previously estimated. However, the clinical course of AKI after CE-CT may not always be so favourable as evidenced by the abovementioned studies. In a prospective observational study concerning 633 emergency department patients undergoing CE-CT without pre-hydration PC-AKI occurred in 70 patients (11%), with persistent renal failure at one-year follow-up in 11 of these patients. (Mitchell, 2015) It should be emphasized that these patients had an emergent indication for CE-CT and might therefore have other risk factors (such as haemodynamic instability) for AKI.

In 5244 patients with ST-Elevation Myocardial Infarction (STEMI) treated with PCI the incidence of PC-AKI for patients with a baseline eGFR of >90, 60-90, 30-59 and <30 ml/min/1.73 m$^2$ was 2.1%, 3.4%, 7.3% and 1.8%, respectively, underlining pre-existent CKD as a risk factor of PC-AKI. (Vavalle, 2016) The relatively low incidence of PC-AKI in the group of patients with an eGFR <30 ml/min/1.73 m$^2$ may be related to the small number of patients (n=89) present in this subgroup. Impaired renal function at presentation and development of PC-AKI were highly associated with worse clinical outcome, including death. A meta-analysis of 39 observational studies including 139,603 participants that investigated cardiovascular outcomes in those with PC-AKI demonstrated an increased risk of mortality, cardiovascular events, renal failure and prolonged hospitalization. (James, 2013) Baseline characteristics that simultaneously predispose to both mortality and PC-AKI were regarded as confounders. The reported incidence of end stage renal disease ranged from 0% to 0.2% in those without PC-AKI and from 0.2% to 4.5% in those with PC-AKI. In a more recent study consisting of 92,317 PCI procedures performed in 90,383 patients the incidence of PC-AKI was 2.3% and of renal replacement therapy 0.3%. (Kooiman, 2015) As expected patients developing PC-AKI had a greater burden

of co-morbidity at baseline and were more likely to have adverse in-hospital outcomes. Using propensity-score based matching (1,371 patients with PC-AKI versus 5,484 patients without PC-AKI) in-hospital major adverse clinical outcomes (in-hospital mortality, cardiogenic shock, heart failure, stroke, bleeding and new requirement for dialysis post-PCI were considerably and significantly higher in AKI versus non-AKI patients and nearly one-third of the in-hospital mortality risk post PCI appeared to be attributable to AKI, demonstrating its clinical importance. (Kooiman, 2015)

In conclusion, the incidence of PC-AKI after intravenous or intra-arterial iodine-containing CM administration in general is low and directly related to the presence and severity of CKD prior to contrast administration and concomitant co-morbidities as demonstrated by propensity-score based matching analyses. The decline in renal function is mostly transient, but in rare instances renal replacement therapy is required with reported incidences of 0.06% after CE-CT and 0.2% to 0.6% post PCI. PC-AKI is a marker of poor outcomes, including increased short- and long-term mortality. Whether there is a causal relation between PC-AKI and poor outcomes remains unclear. However, reducing the incidence of PC-AKI in high risk patients (such as those undergoing emergent PCI, or with an eGFR <30 ml/min/1.73m$^2$) by optimal risk stratification and preventive measures, remains a major goal in clinical practice.

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

Since this guideline only uses a single cut-off value of eGFR <30 ml/min/1.73m$^2$ for preventive IV hydration, the distinction between IV or IA iodinated CM is largely theoretical and has no prevention consequences. Therefore, both IV and IA iodinated CM administration will be referred to by the general term **"intravascular CM administration"**.

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## Verantwoording

Laatst beoordeeld : 01-07-2017

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

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# Risicostratificatie en stratificatietools

## 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 CM krijgen toegediend.

Beschouw het risico van PC-AKI vergelijkbaar bij laagosmolaire 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.

Patients with a kidney transplantation and risk of PC-AKI

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

Solitary kidney and risk of PC-AKI

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

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

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

Contrast medium dose and risk of PC-AKI

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

For intra-arterial iodine-containing CM administration, and especially for interventional procedures, the CM dose with regard to PC-AKI is critical above a certain level. It has been advocated by Nyman et al. to use the *absolute* eGFR that is corrected for body surface area (see also chapter 5) and that the risk of PC-AKI is limited when the administered iodine dose (in gram iodine) to eGFR ratio remains below 1.1 (Nyman, 2008). In the cardiology literature Gurm et al. indicate that the risk of PC-AKI is increased above a CM volume to creatinine clearance (or eGFR) ratio of 3.0. This corresponds at a cut-off level of eGFR 45 ml/min/1.73m$^2$ 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 |

## Onderbouwing

## Achtergrond

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 / Summary of Findings

*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.<br><br>*(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.<br><br>*(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.<br><br>*(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.<br><br>*(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?*

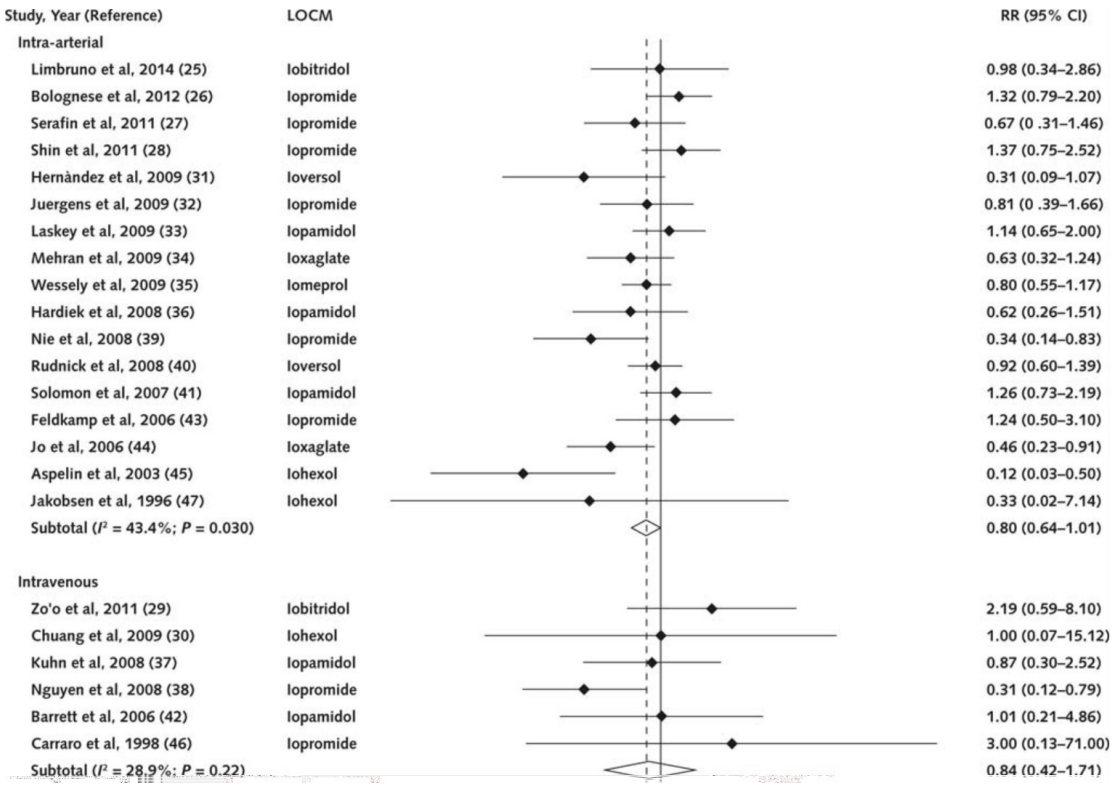
Description of studies

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**




*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

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

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# Evaluatie van 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 CM 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 CM-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

## Onderbouwing

## Achtergrond

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 anc 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

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

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# Prevention van PC-AKI

This module consists of seven submodules.

## Verantwoording

Laatst beoordeeld : 01-11-2017

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

# Hydratie en complicaties

## Uitgangsvraag

Welke hydratiestrategie dient te worden toegepast bij patiënten die intravasculair jodiumhoudend contrastmiddel (CM)-toediening ondergaan en een hoog PC-AKI risico hebben?

*Subvragen*

1. Is er een significant verschil in de incidentie van PC-AKI bij hydratie versus geen hydratie?
2. Is er een significant verschil in de incidentie van PC-AKI bij orale versus intraveneuze pre- en posthydratie?
3. Is er een significant verschil in de incidentie van PC-AKI bij intraveneuze NaCl versus NaHCO3?
4. Is er een significant verschil in de incidentie van PC-AKI bij intraveneuze prehydratie (alleen) versus pre- en posthydratie (gecombineerd)?
5. Is er een significant verschil in de incidentie van PC-AKI bij patiënten die gecontroleerde diurese ondergaan versus standaard hydratieschema's?

## 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.

## Onderbouwing

## Achtergrond

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 / Summary of Findings

| | |
|---|---|
| **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.<br><br>*(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/1.73$m^2$.<br><br>*(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.<br><br>*(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.<br><br>*(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.<br><br>*(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.<br><br>*(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**

| | Bicarbonate - ss | | Saline - ss | | | Risk Ratio | Risk Ratio |
|---|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | 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)

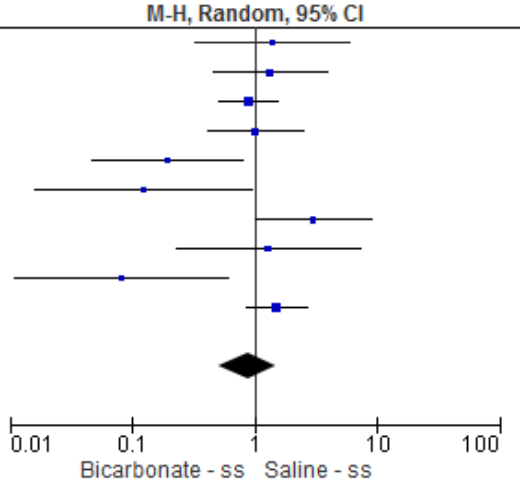


**Figure 2 Pooled analysis of PC-AKI risk in patients receiving short schedules for bicarbonate versus long schedule for saline for CAG/PCI.**

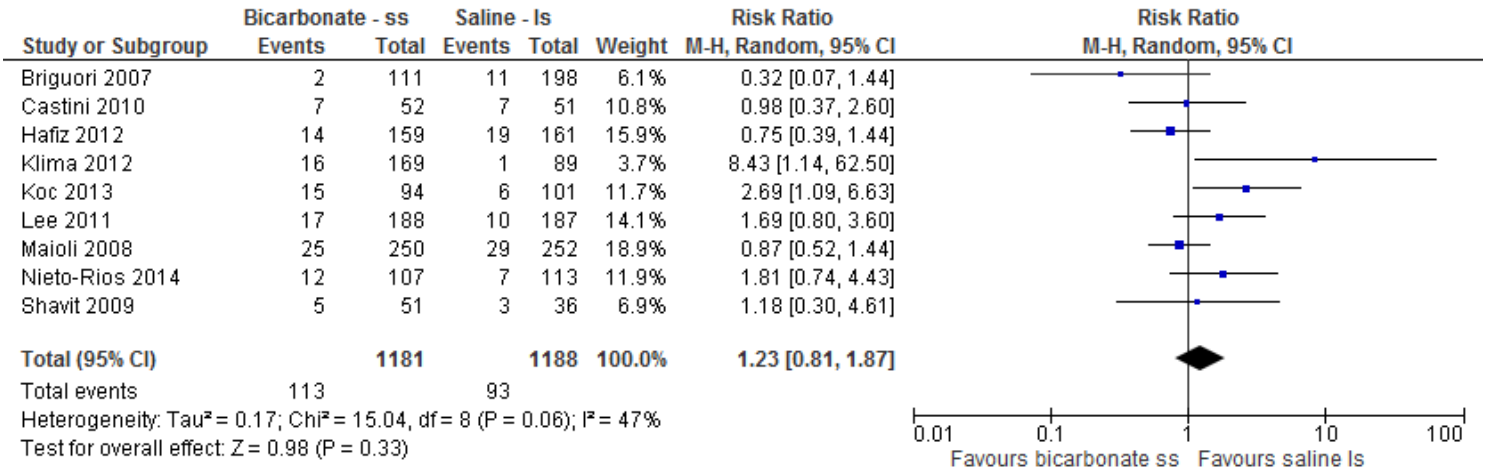


**Table 1 Adverse events in bicarbonate versus saline infusion or controlled hydration versus standard hydration.**

## 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

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

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# Statines en hydratie tegen PC-AKI

## Uitgangsvraag

Dienen statines te worden aanbevolen naast hydratie om de kans om PC-AKI te verkleinen bij patiënten met chronische nierschade die intravasculair jodiumhoudend contrastmiddel (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.

## Onderbouwing

## Achtergrond

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 / Summary of Findings

| | |
|---|---|
| **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.<br><br>*(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<br><br>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<br>Mortality: 0<br>Start dialysis: 0<br>ICU admission: NR | PC-AKI: 3.<br>Mortality: (<br>Start dialys<br>1<br>ICU admission: NR |

| | | | | | | |
|---|---|---|---|---|---|---|
| Toso, 2010 | CrCL<60 mL/min<br><br>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<br>Mortality: 1<br>Start dialysis: 0<br>ICU admission: NR | PC-AKI: primary 11/second 15<br>Mortality: (<br>Start dialys 1<br>ICU admission: NR |
| Patti, 2011 | sCr ≤3mg/dl, subgroup with pre-existing renal failure: serum creatinine level ≥1.5mg/dl or CrCl≤60.<br><br>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<br>Mortality: NR<br>Start dialysis: NR<br>ICU admission: NR | PC-AKI: 25<br>Mortality: I<br>Start dialys NR<br>ICU admission: NR |

| | | | | | | |
|---|---|---|---|---|---|---|
| Quintavalle, 2012 | eGRF≤60mL/min/1.73m$^2$<br><br>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<br>Mortality: NR<br>Start dialysis: NR<br>ICU admission: NR | PC-AKI: 7<br>Mortality: I<br>Start dialys<br>NR<br>ICU admission:<br>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.<br><br>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<br>Mortality: NR<br>Start dialysis: NR<br>ICU admission: NR | PC-AKI: 4.<br>Mortality: I<br>Start dialys<br>NR<br>ICU admission:<br>NR |

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|---|---|---|---|---|---|---|
| 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.<br><br>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<br>Mortality: NR<br>Start dialysis: NR<br>ICU admission: NR | PC-AKI: 21<br>Mortality: I<br>Start dialys<br>NR<br>ICU admission: NR |
| Abaci, 2015 | 30≤eGRF≤60 mL/min/1.73m$^2$.<br><br>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<br>Mortality: NR<br>Start dialysis: NR<br>ICU admission: NR | PC-AKI: 8.<br>Mortality: I<br>Start dialys<br>NR<br>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<br>Mortality: NR<br>Start dialysis: 0<br>ICU admission: NR | PC-AKI: 20<br>Mortality: I<br>Start dialys<br>0<br>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<br>Mortality: NR<br>Start dialysis: 0<br>ICU admission: 0 | PC-AKI: 3<br>Mortality: I<br>Start dialys<br>0<br>ICU admission: |

*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

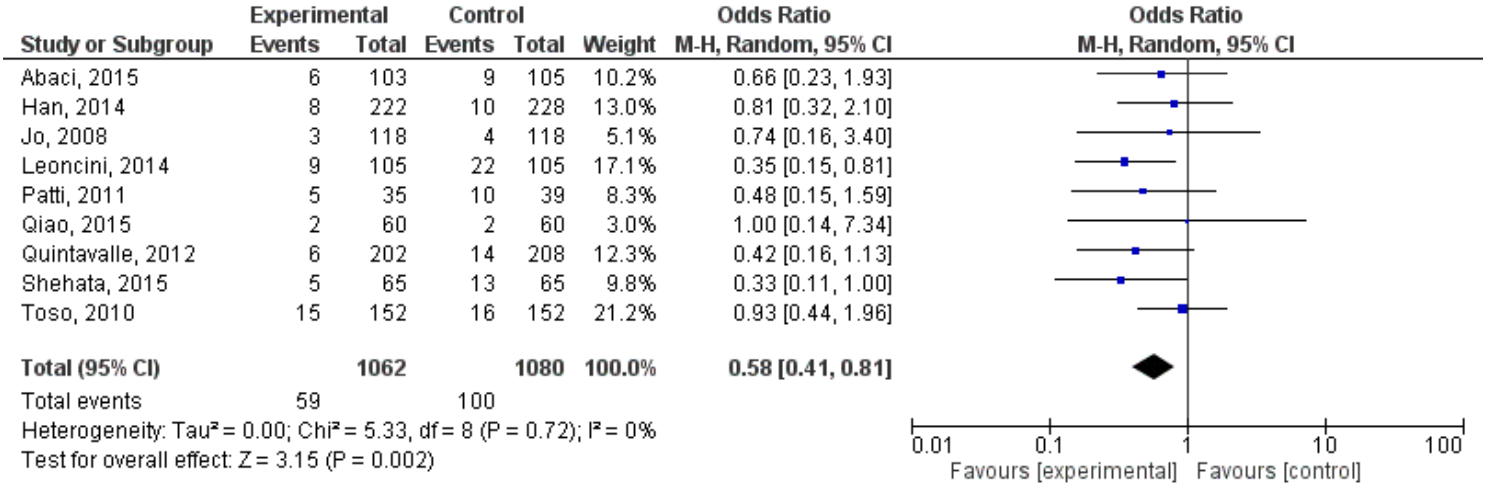
control group developed PC-AKI after the procedure.

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.

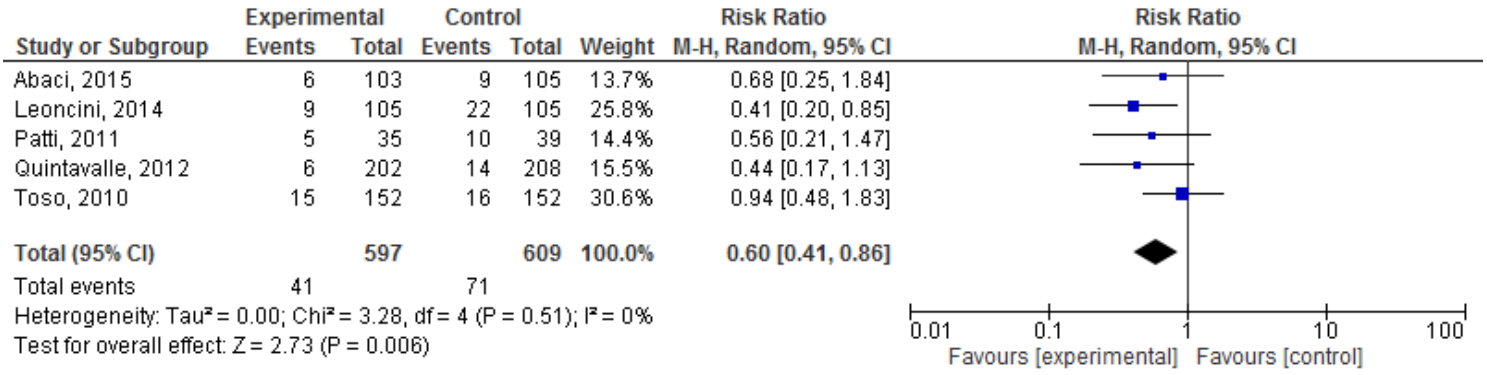
**Figure 1 Meta-analysis of studies in patients undergoing coronary angiography/percutaneous interventions**




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**



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

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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# Prophylaxe met NAC en hydratie tegen PC-AKI

## 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 contrastmiddel (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.

## Onderbouwing

## Achtergrond

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 / Summary of Findings

| | |
|---|---|
| **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.<br><br>*(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.<br><br>*(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.<br><br>*(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.<br><br>*(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)

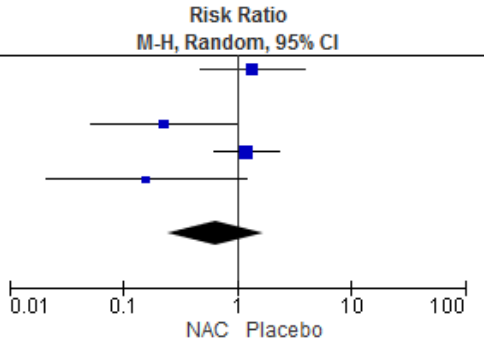



**Figure 2 Meta-analysis of NAC vs Placebo in Coronary angiography with intra-arterial CM administration in patients with normal kidney function**

| 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)

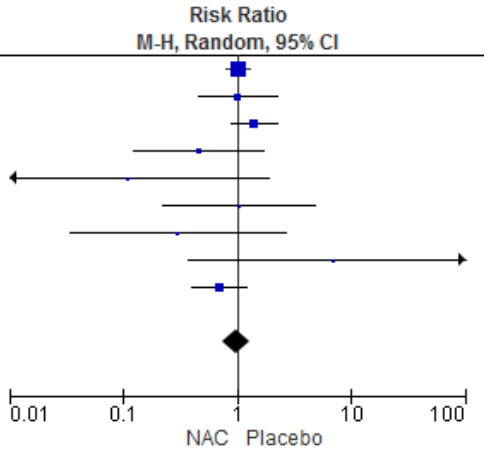
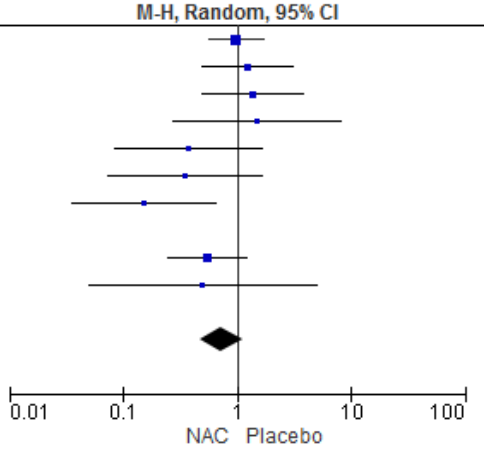



**Figure 3 Meta-analysis of NAC vs Placebo in Coronary angiography with intra-arterial CM administration in patients with eGFR <60 ml/min/1.73m$^2$.**

| 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

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

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# Vitamine C en hydratie tegen PC-AKI

## 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 contrastmiddel (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.

## Onderbouwing

## Achtergrond

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 / Summary of Findings

| | |
|---|---|
| **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.<br><br>*(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,<br>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<br>500 ml during/after for 6-h | 6.8 | 4.3 |
| Zhou 2012 | China | SCr >97 mmol/L | 3 g iv morning of procedure<br>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<br>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<br>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<br>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.

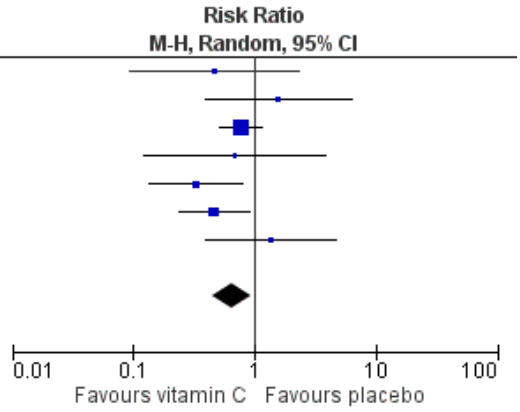
Two other meta-analyses are presented as well in the Appendix. One that includes the studies that appeared in abstract form as well (figure 2) and one that includes all RCTs on vitamin C (figure 3). Both demonstrate a similar effect as the meta-analysis in figure 1.

**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 | | | |

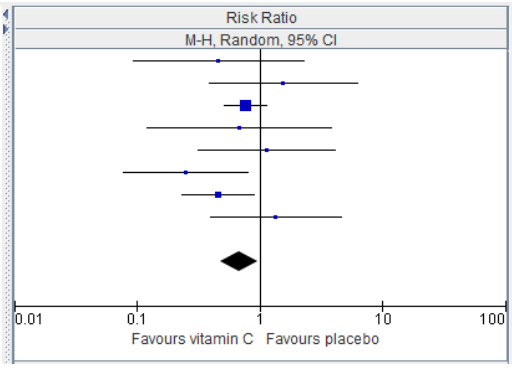
Heterogeneity: Tau² = 0.03; Chi² = 6.99, df = 6 (P = 0.32); I² = 14%
Test for overall effect: Z = 2.41 (P = 0.02)




## 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% CI |
|---|---|---|---|---|---|---|
| Albabtain 2013 | 2 | 57 | 5 | 66 | 4.4% | 0.46 [0.09, 2.30] |
| Boscheri 2007 | 5 | 74 | 3 | 69 | 5.7% | 1.55 [0.39, 6.26] |
| Brueck 2011 | 24 | 98 | 62 | 193 | 43.1% | 0.76 [0.51, 1.14] |
| Dvorsak 2013 | 2 | 40 | 3 | 41 | 3.8% | 0.68 [0.12, 3.88] |
| Komiyama 2011 | 5 | 78 | 4 | 71 | 6.8% | 1.14 [0.32, 4.07] |
| Li 2012 | 3 | 35 | 12 | 35 | 7.9% | 0.25 [0.08, 0.81] |
| Spargias 2004 | 11 | 118 | 23 | 113 | 21.0% | 0.46 [0.23, 0.90] |
| Zhou 2011 | 6 | 82 | 4 | 74 | 7.3% | 1.35 [0.40, 4.61] |
| Total (95% CI) | | 582 | | 662 | 100.0% | 0.68 [0.48, 0.96] |
| Total events | 58 | | 116 | | | |

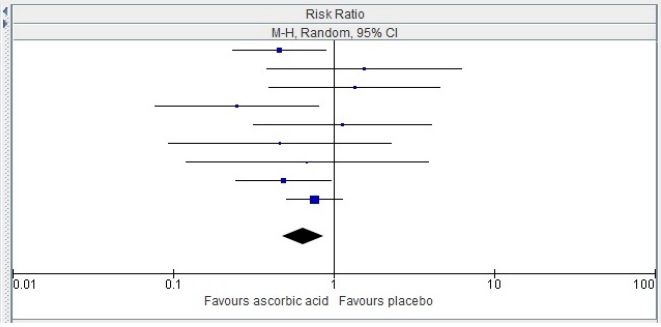
Heterogeneity: Tau² = 0.03; Chi² = 7.85, df = 7 (P = 0.35); I² = 11%
Test for overall effect: Z = 2.19 (P = 0.03)




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

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

Heterogeneity: Tau² = 0.02; Chi² = 8.67, df = 8 (P = 0.37); I² = 8%
Test for overall effect: Z = 2.88 (P = 0.004)




## 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

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

## Referenties

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# Nefrotoxische medicatie en PC-AKI

## Uitgangsvraag

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

## Aanbeveling

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

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

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.

## Onderbouwing

### Achtergrond

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 / Summary of Findings

| | |
|---|---|
| **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.<br><br>*(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.<br><br>*(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.<br><br>*(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

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.

# Profylactische nierfunctievervangende therapie tegen PC-AKI

## Uitgangsvraag

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

## Aanbeveling

Gebruik geen profylactische hemodialyse bij niet dialyse-afhankelijke patiënten met chronische nierschade stadium 4-5, die intravasculair jodiumhoudend CM 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 CM 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 CM toegediend krijgen. (In andere woorden: bij het inplannen van een onderzoek met jodiumhoudend CM hoeft er geen rekening gehouden worden met het dialyseschema van de patiënt.)

## 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.

## Onderbouwing

## Achtergrond

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)**

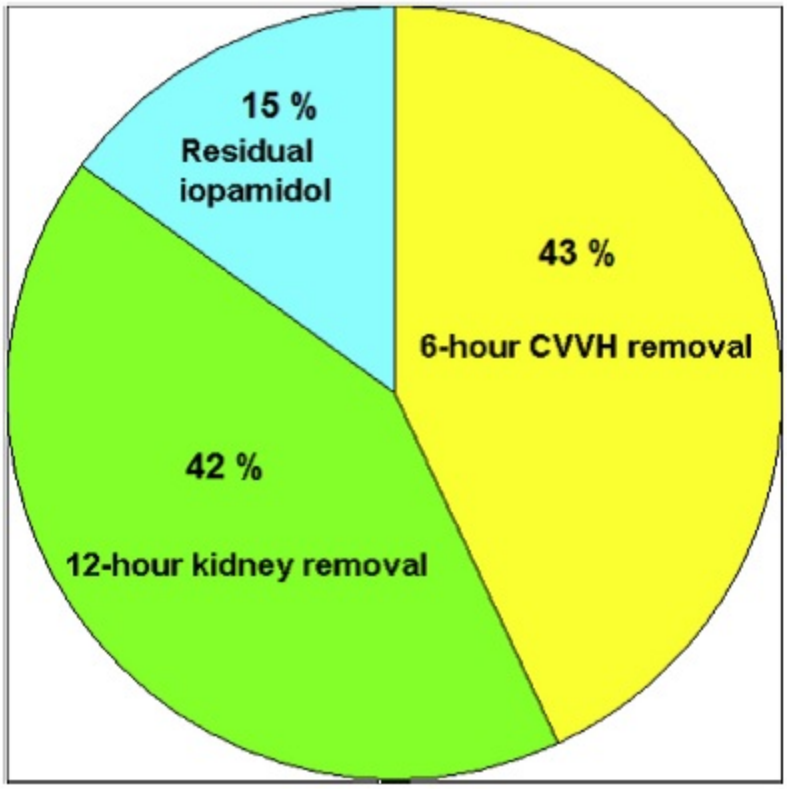



Figure 2. Iopamidol removal (expressed as percentage of total infused dose) by 6-hour CVVH and 12-hour diuresis. Residual iopamidol represents the difference between total infused iopamidol and total iopamidol removed by both kidney and CVVH.

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 / Summary of Findings

| | |
|---|---|
| **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.<br><br>*(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.<br><br>*(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.<br><br>*(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.<br><br>*(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%<br>10%<br>20% | NR<br>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%<br>10% | 14%<br>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.<br>19% | NR<br>NR | 16%<br>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**

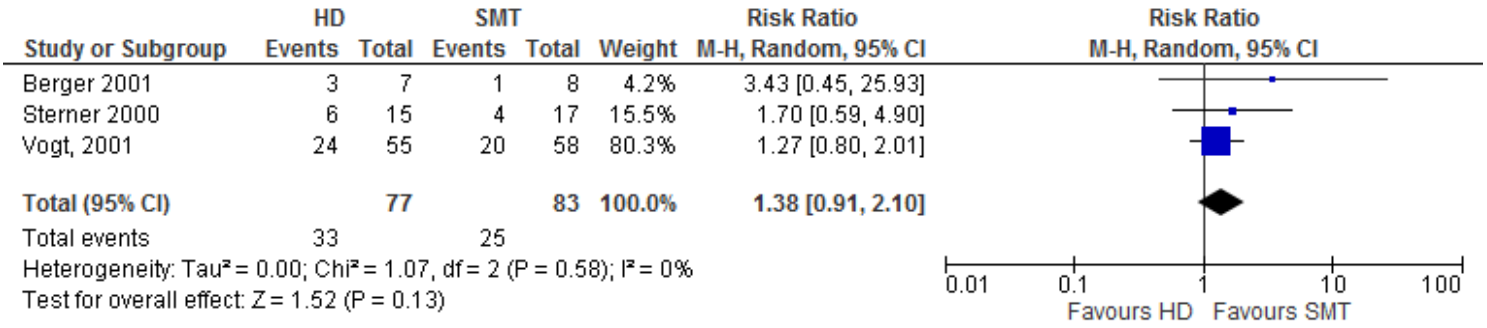
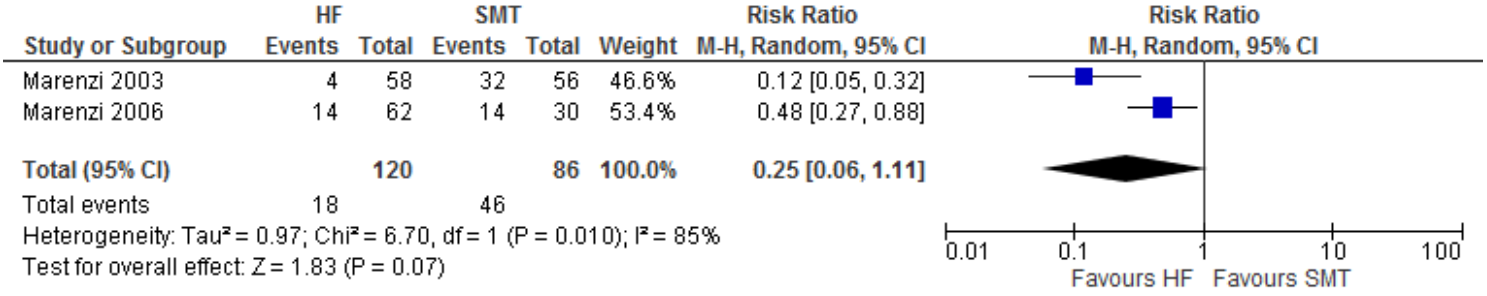



**Figure 3 Pooled analysis of PC-AKI risk in CKD 4-5 patient undergoing CAG and/or PCI and receiving either HF or SMT**




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 3$^{rd}$ 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

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

## Referenties

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# Nefrotoxiciteit van GBCA

## Uitgangsvraag

Hoe kan post-contrast acute nierschade (PC-AKI) worden voorkomen bij toediening van Gadolinium-Based Contrast Agents (GBCA)?

*Subvragen*

1. Is toediening van GBCA geassocieerd met een toegenomen risico op PC-AKI vergeleken met placebo/niet-versterkte beeldvorming?
2. Is er een verschil in het risico op PC-AKI tussen hoge en lage dosering GBCA?
3. Is er een verschil in het risico op PC-AKI tussen verschillende GBCA?

## Aanbeveling

Maak een individuele risico-batenanalyse met de aanvragende arts en nefroloog van de patiënt om te zorgen voor een strikte indicatie voor gadolinium-versterkte MRI met lineaire GBCA bij patiënten met eGFR < 30 ml/min/1,73m2.

Gebruik de optimale GBCA dosis gebaseerd op gewicht van de patiënt die nodig is om een diagnostische MRI te verrichten in lokale doseringsprotocollen.

Pas geen profylactische maatregelen toe om PC-AKI te voorkomen bij hoog-risico patiënten (eGFR<30ml/min/1.73m*2*) die GBCA IV krijgen in een standaarddosis.

Vervang geen ICM door GBCA om PC-AKI te voorkomen bij CT en/of DSA.

## Overwegingen

Compared to the large amount of literature of the incidence and prevention of PC-AKI after administration of Iodine-based contrast media (ICM), little is known on this subject after administration of GBCA. In general, it is said that GBCA are less nephrotoxic than ICM, and the above-described literature seems to acknowledge that.

It is generally recommendable to use the lowest GBCA dose needed to achieve a diagnostic examination, and usually the standard dose of 0.1 mmol/kg suffices for most clinical indications (ESUR 2017).

Looking more deeply into the chemistry of CM and the results of experimental studies, another picture emerges (Nyman, 2002). First of all, ICM concentrations are expressed in mgI/ml and GBCA concentrations in mmol/ml, a fundamental difference. One mol of Iodine atoms corresponds to 126.9g of I, whereas 1 mol of Gd atoms corresponds to 157.3g of Gd. As most of the commercially available GBCA are 0.5mmol/ml, they thus contain 78.65 mg/ml of Gd. When it comes to Iodine, 0.5mmol/ml I, corresponds to 63mgI/ml. But ICM are usually used in concentrations ranging from 300mg/ml - 400mg/ml, i.e. 2.36mmol/ml - 3.15 mmol/ml. The commercially available iodine doses are thus much higher than the commercially available gadolinium doses (Nyman, 2002).

Furthermore, GBCA contain one attenuating Gd atom per molecule, whereas ICM monomers contain 3 attenuating I atoms per molecule and ICM dimers contain 6 attenuating I atoms per molecule. The combination of more attenuating atoms per molecule and the difference in attenuation of Gd and I at different photon energies, results in the fact that at 120 kVp CT, approximately 110mgI/ml monomer equally attenuates with 0.5mmol/ml Gd. At 80kVp CT, approximately 95mgI/ml monomer equally attenuates with 0.5mmol/ml Gd (Nyman 2002). For DSA a concentration of 60 to 80mg/ml I monomer, produces the same attenuation as 0.5mmol/l GBCA at commonly used 70-90 kVp range (Nyman, 2002).

Thus, in order to achieve the same amount of attenuation in CT with an ICM monomer 300mg/ml, a triple Gd 0.5mmol/ml dose has to be administered. This also means that DSA attenuation produced by an ICM monomer 300mg/ml is achieved with a 4 - 5 times higher Gd 0.5mmol/ml dose. The above results show that changing from ICM to GBCA in CT and DSA is not a safe option due the 3 to 5 times higher GBCA doses necessary to achieve the same amount of attenuation.

Therefore, the working group concludes that, especially in interventional radiology, using GBCA would potentially lead to more harmful effects compared to ICM, and would not recommend substituting ICM with GBCA. This is in line with a systematic review in which the authors concluded that GBCA does not appear to be safer than iodinated contrast in patients at risk of PC-AKI (Boyden, 2008).

As the dose to achieve significant enhancement for GBCA in MRI is much lower as in CT and DSA, it is not a surprise that the small amount of available literature shows no indication of PC-AKI after the administration of GBCA at the recommend standard dose of 0,1 mmol/kg.

Therefore, the working group sees no additive value in using any prophylactic measures (such as hydration, as described in part 1 of the guideline), and recommends not to use any. A recent Canadian guideline on GBCA in chronic kidney disease states that a standard dose of GBCA in patients with eGFR 30 to 60 is safe and no additional measures are necessary. In patients with eGFR <30 ml/min/1.73m$^2$ and patients on dialysis, administration of GBCA should be considered individually (Schieda, 2019). Thus an individual risk-benefit analysis with the patient's requesting physician and nephrologist should be made to ensure a strict indication for gadolinium-enhanced MRI with linear agents in patients with eGFR < 30 ml/min/1.73m$^2$.

## Onderbouwing

## Achtergrond

From laboratory testing on cell lines and animals, it is known that Gd chelates are nephrotoxic. In daily practice, this nephrotoxicity is not an issue, as the required dose of these chelates is usually too low to lead to nephrotoxicity in patients.

## Conclusies / Summary of Findings

| | |
|---|---|
| **Very low GRADE** | Administration of macrocyclic gadolinium-based contrast agents does not seem to be associated with an increased risk of PC-AKI.<br><br>*Sources: (Deray, 2013; Kroencke 2001; Tombach 2001; Tombach 2002)* |

| | |
|---|---|
| **Very low GRADE** | Administration of linear gadolinium-based contrast agents does not seem to be associated with an increased risk of PC-AKI.<br><br>*Sources: (Broome 2007; Deray, 2013; Gok Oguz, 2013; Kittner 2007; Naito 2017; Townsend, 2000; Trivedi, 2009)* |

| | |
|---|---|
| **Very low GRADE** | It is unknown whether administration of macrocyclic gadolinium-based contrast agents is associated with an increased requirement of dialysis.<br><br>*Source: (Deray, 2013)* |

| | |
|---|---|
| **Very low GRADE** | It is unknown whether administration of linear gadolinium-based contrast agents is associated with an increased requirement of dialysis.<br><br>*Source: (Townsend, 2000)* |

| | |
|---|---|
| **Very low GRADE** | There seems to be no dose-response association between macrocyclic gadolinium-based contrast agents and PC-AKI.<br><br>*Sources: (Kroencke, 2001; Tombach, 2001; Tombach, 2000)* |

| | |
|---|---|
| **Very low GRADE** | There seems to be no dose-response association between gadolinium-based contrast agents and PC-AKI.<br><br>*Sources: (Broome 2007; Kittner 2007)* |

| | |
|---|---|
| **Very low GRADE** | It is unknown whether there is a difference in the risk of PC-AKI between different gadolinium based contrast agents<br><br>*Source: (Naito, 2017)* |

## Samenvatting literatuur

1. Gadolinium- Based Contrast Agents versus placebo/unenhanced imaging

*Macrocyclic GBCA*

Deray (2013) describe a prospective multicentre non-randomized study, comparing the renal safety of Gd-DOTA (macrocyclic GBCA) enhanced MRI with non-enhanced MRI in 114 patients with eGFR 15 - 60

ml/min/1.73 $m^2$(Deray, 2013).Gd-DOTA was injected intravenously by a power injector at a dose of 0.1 mmol/kg. PC-AKI was defined as an increase in SC of at least 25% or 44.2mmol/kg above the baseline value. Serum creatinine levels were measured 72±24 hours after the MRI.

*Linear GBCA*
In a randomized controlled trial by Townsend (2000) 32 patients were included. They were divided into 2 categories, eGFR 30-60 (group 1) and eGFR 10 to 29 ml/min/1.73$m^2$ (group 2) (Townsend, 2000). Patients in both groups were randomized to be infused with either Gd-BOPTA (linear GBCA) or saline, both at a dose of 0.2 mmol/kg. Both groups maintained saline infusion after the initial bolus and received a total of 250-300 ml saline. No MRI took place after the injection. PC-AKI was defined as an increase in serum creatinine (SC) > 44,2 µmol/l above the baseline value. SC was measured before the injection and for 7 consecutive days after the injection. In group 1, 9 patients received Gd and 6 saline, in group 2, 11 patients received Gd and 6 saline.

Gok Oguz (2013) describes 144 patients with 1 or more risk factors for AKI (advanced age (> 75 years), diabetes mellitus, chronic kidney disease, congestive heart failure, using other nephrotoxins, and hypotension) in a prospective case-control study (Gok Oguz, 2013). Patients were divided into 2 groups, but the article does not state clearly what the criteria are to be included in either one of the groups. All 72 patients (mean eGFR 36 ml/min/1.73$m^2$) in group 1 received intravenous injection with Gd-DTPA (linear GBCA), whereas all 72 patients (mean eGFR 39 ml/min/1.73$m^2$) in group 2 received no Gd contrast. PC-AKI was defined as an increase of SC of at least 26.4 µmol/l or ≥ 50% from baseline. Before the MRI and at 6 h, 24 h, 72 h, and 168 h after the MRI, SC was measured.

Trivedi (2009) describe a retrospective study that included 162 patients who underwent MRI with gadodiamide (linear GBCA) and 125 controls that underwent unenhanced MRI (Trivedi, 2009). Patients were included when SC measurements were available during 7 days preceding MRI and 48 to 72 hours after MRI. Baseline eGFR was 103.1 +/- 49.5 ml/min/1.73$m^2$ in the group receiving Gd and 103.4 +/- 48.4 ml/min/1.73$m^2$ in the control group. PC-AKI was defined as SC >44.2 micromol/l compared to baseline.

Results
*Outcome Post-Contrast Acute Kidney Injury (PC-AKI)*
Four studies (Townsend, 2000, Deray, 2013, Gok Oguz, 2013 and Trivedi, 2009) reported on the incidence of PC-AKI after administration of GBCA. Due to the heterogeneity in study designs the results were not pooled.

*Macrocyclic GBCA*
Deray (2013) reported PC-AKI in one patient after injection with macrocyclic Gd-DOTA (1.4%).

*Linear GBCA*
There were no cases of PC-AKI in the studies Gok Oguz (2013), Townsend (2000) and Trivedi (2015) using a variety of linear GBCA.
Quality of evidence
The quality of certainty of evidence was graded as very low due to high risk of bias (see Table Risk of Bias assessment, downgraded by one point) and low number of patients (imprecision downgraded by two points).

Outcome Dialysis

Two studies reported on the requirement of dialysis after administration of GBCA. Both studies (Townsend, 2003 (linear GBCA) and Deray, 2013 (Macrocyclic GBCA)) reported that no subjects required dialysis.

Quality of evidence

The quality of certainty of evidence was graded as very low due to the low number of patients (imprecision downgraded by two points).

No studies reported on the outcome mortality.

2. High versus low dose of Gadolinium-Based Contrast Agents

*Macrocyclic GBCA*

Kroencke (2001) randomized 94 patients with suspected abnormality of the abdominal aorta or renal arteries to MR angiography after the IV injection of one of four doses of gadobenate dimeglumine (0.025, 0.05, 0.1, and 0.2 mmol/kg of body weight), a macrocyclic GBCA (Kroencke, 2001). SC was obtained pre-dose and at the 24-hr follow-up examination.

Tombach (2001) describe 21 patients in a randomized controlled, open-label trial. Patients were classified into two subgroups according to their creatinine clearance: group 1 (*n*=12), eGFR 30 to 80 ml/min/1.73m$^2$ and group 2 (*n* =9), eGFR<30 ml/min/1.73m$^2$(Tombach, 2001). Then, patients were randomly assigned to receive the higher dose of 0.3 mmol/kg of the macrocyclic GBCA gadobutrol (group 1, *n*=6/12; group 2, *n*=4/9) or the lower dose of gadobutrol of 0.1 mmol/kg (group 1, *n*=6/12; group 2,*n*=5/9). Changes in vital signs, clinical chemistry, and urinalysis results, including creatinine clearance, were monitored before, at 6 hours, and then every 24 hours until 72 hours (group 1) or 120 hours (group 2) after intravenous injection of gadobutrol.

Tombach (2002) enrolled 11 patients with end-stage renal failure who required haemodialysis treatment (Tombach, 2002). Purpose of the study was to assess the safety and dialysability of gadobutrol. Gadobutrol (1 mol/L) was injected intravenously at randomly assigned doses of either 0.3 or 0.1 mmol of gadolinium per kilogram of body weight for contrast-enhanced MR imaging.

*Linear GBCA*

Kittner(2007) randomized patients with suspected renal artery stenosis to 0.01, 0.05, 0.1, or 0.2 mmol/kg of the linear GBCA gadodiamide (n=69, 67, 69 and 61, respectively) (Kittner, 2007).Safety of gadodiamide was monitored by comparing the data of 12-lead ECGs, vital signs (blood pressure, body temperature, heart and respiratory rate), serum biochemistry (including renal parameters), and physical examinations collected immediately before and 24 h after gadodiamide administration.

Broome (2007) retrospectively studied the dialysis and MRI records (Broome, 2007). One hundred eighty six dialysis patients underwent 559 MRI exams; including 301 Gd enhanced MRI between 2000 and 2006. The linear GBCA gadodiamide was the sole Gd chelate used in either 0.1 mmol/kg or 0.2 mmol/kg.

Results

*Outcome Post-Contrast Acute Kidney Injury (PC-AKI)*

Five studies reported on the incidence of PC-AKI (Kroencke, 2001; Tombach, 2001, Tombach, 2002, Kittner, 2007 and Broome 2007). All five studies reported no cases of PC-AKI, using either linear or macrocyclic GBCA.

Quality of evidence
The quality of certainty of evidence was graded as very low due to high risk of bias (see Table Risk of Bias assessment, downgraded by one point) and the low number of patients (imprecision downgraded by two points).

No studies reported on the outcomes dialysis and mortality.

3. Nephrotoxicity of different gadolinium-based contrast agents
One study investigated the difference in nephrotoxicity between different gadolinium-based contrast agents.

Naito (2017) describes a prospective randomized study including 102 patients that were randomized to either receive 0.1 mmol/kg gadodiamide (linear GBCA) or 0.1 mmol/kg Gd-DTPA (linear GBCA) (Naito, 2017). eGFR in the gadodiamide group was 90.5 +/- 19.5 ml/min/1.73m$^2$ and 94.1 +/- 26.4 ml/min/1.73m$^2$ in the Gd-DTPA group. SC was measured 16-80 hour after the procedure. PC-AKI was defined as SC ≥ 44.2 micromol/l or ≥ 30% above baseline.

Results
*Outcome Post-Contrast Acute Kidney Injury (PC-AKI)*
In both groups, no PC-AKI occurred.

Quality of evidence
The quality of certainty of evidence was graded as very low due to high risk of bias (see Table Risk of Bias assessment, downgraded by one point) and the low number of patients (imprecision downgraded by two points).

No studies reported on the outcomes: dialysis and mortality.

## Zoeken en selecteren

To answer our clinical question a systematic literature analysis was performed.

**P (Patient)** Patients who received Gadolinium-Based Contrast Agents (GBCA).
**I (Intervention)** Gadolinium based contrast agents, gadoterate meglumine, gadodiamide, gadobenate dimeglumine, gadopentetate dimeglumine, gadoteridol, gadoversetamide, gadobutrol.
**C (Comparison)** No GBCA or another type of GBCA, gadoterate meglumine, gadodiamide, gadobenate dimeglumine, gadopentetate dimeglumine, gadoteridol, gadoversetamide, gadobutrol.
**O (Outcomes)** Nephrotoxicity (acute and permanent), dialysis, mortality.

Relevance of outcome measures

The working group considered the outcomes nephrotoxicity, mortality and dialysis critical measures and outcome for the decision-making process.

The working group did not define the criteria for the outcomes a priori, but used the outcomes as defined in the studies. The working group considered a clinically relevant difference according to the standards of GRADE: a difference in relative risk of 25% for dichotomous outcomes and a difference of 10% for continuous outcomes (GRADE handbook, web-link in references).

Methods
The databases Medline (OVID), Embase and the Cochrane Library were searched from 1st of January 1996 to March 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). The literature search produced 245 hits: 22 SR, 51 RCTs and 172 OBS. Based on title and abstract a total of 15 studies were selected. After examination of full text 7 articles were selected: 4 for subquestion 1, 2 for subquestion 2 and 1 for subquestion 3. Reasons for exclusion are reported in exclusion table (under the Tab "exclusion table"). The most relevant study characteristics of the included studies can be found in the evidence tables.

## Verantwoording

Laatst beoordeeld : 24-06-2020

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

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# Hypersensitiviteitsreacties

This module consists of six submodules.

## Verantwoording

Laatst beoordeeld :

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

# Introductie hypersensitiviteitsreacties

## Introduction to Hypersensitivity Reactions to Contrast Media

*Disclaimer: This narrative review has been written by members of the Guideline Development Group so that non-specialized readers can follow the Modules about Hypersensitivity more easily. It was not part of the actual guideline process with structured literature analyses.*

The increased use of contrast media (CM) may give rise to an increased absolute number of total hypersensitivity reactions (HSR). The relative number of immediate HSR has decreased since the introduction of nonionic, low-osmolar ICM, while the number of non-immediate HSR is on the rise, due to an increased use of iso-osmolar ICM (Rosado Ingelmo, 2016).

**Terminology and Definitions (see also 'Definitions of Adverse Drug Reactions')**
The following definitions and terminology are based on the standard terminology recommended by the World Allergy Organisation (Cordona, 2020; Demoly, 2014; Johansson, 2004). When dealing with CM, the term allergy should be avoided as much as possible.

*Hypersensitivity:* Objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus that is tolerated by normal subjects.

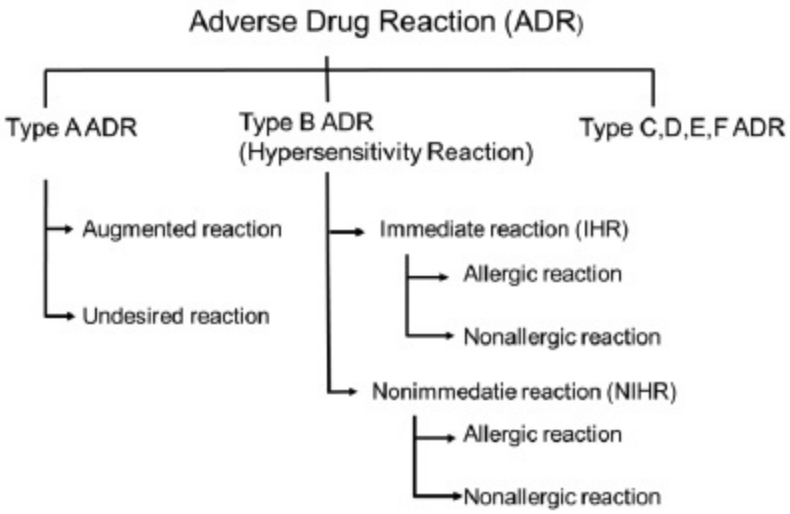
*Drug Hypersensitivity Reaction (DHR)*: adverse effects of drugs that clinically resemble allergic reactions ('pseudo-allergic'). These include adverse reactions that are immune or nonimmune mediated.

*Drug Allergy:* Hypersensitivity reactions that are associated with an immune mechanism for which evidence can be shown in the form of drug-specific antibodies or activated T lymphocytes.

*Immediate (acute, early) hypersensitivity reaction to contrast media:* an adverse reaction that occurs within 1 hour of contrast agent injection. Acute reactions can either be allergy-like (IgE-mediated or not) hypersensitivity reactions or chemotoxic responses.

*Non-immediate (delayed, late) hypersensitivity reaction to contrast media:* an adverse reaction that occurs between 1 hour and 1 week after contrast agent injection.

**Figure 1 Schematic of adverse drug reaction types**




*Adverse drug reaction (ADR):* a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man (WHO definition) (See Figure 1 Schematic of adverse drug reaction types).

ADR can be classified in multiple types, and for contrast media types A, B and D are most relevant. Type A (augmented) reactions result from an exaggeration of a drug's normal pharmacological actions when given at the usual therapeutic dose and are normally dose dependent. These include all physiologic reactions. Type B (bizarre) reactions are novel responses that are not expected from the known pharmacological actions of the drug. These are less common, and so may only be discovered for the first time after a drug has already been made available for general use. These include allergic or non-allergic hypersensitivity reactions. Type D, or 'delayed' reactions, become apparent sometime after the use of a medicine. The timing of these may make them more difficult to detect. These include Nephrogenic Systemic Fibrosis (NSF) or iodine-induced hyperthyroidism (Edwards, 2000).

*Anaphylaxis:* Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes (Cordona, 2020; WHO ICD-11 definition).

Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled (Cordona, 2020):
1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
And at least one of the following:

a. Respiratory compromise (e.g., dyspnoea, wheezing/bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
c. Severe gastrointestinal symptoms (e.g., severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens

2. Acute onset of hypotensiona or bronchospasmb or laryngeal involvementc after exposure to a known or highly probable allergend for that patient (minutes to several hours), even in the absence of typical skin

involvement.

Note: a hypotension defined as a decrease in systolic BP greater than 30% from that person's baseline, or a systolic BP less than <90 mmHg. b. Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause “inhalational” reactions in the absence of ingestion. c. Laryngeal symptoms include stridor, vocal changes, odynophagia. d. An allergen is a substance (usually a protein) capable of triggering an immune response that can result in an allergic reaction. Most allergens act through an IgE-mediated pathway, but some non-allergen triggers can act independent of IgE (for example, via direct activation of mast cells).

**Immediate hypersensitivity reactions to contrast media**

Pathophysiology

Hypersensitivity reactions to CM are poorly understood. Recent research suggests that hypersensitivity reactions to nonionic CM are a heterogeneous disease. It can develop from multiple mechanisms such as IgE-dependent, complement dependent, direct membrane effects of CM, and possibly other mechanisms that have not been identified yet (Zhai, 2017). When an allergic drug reaction is suspected, DHR is the preferred term, because true drug allergy and nonallergic DHR may be difficult to differentiate based on the clinical presentation alone, especially in cases of acute severe DHR (Demoly, 2014).

Allergy-like hypersensitivity reactions may or may not be truly IgE-mediated. In general, allergy can be either antibody- or cell-mediated. Cell-mediated reactions usually occur after one or several days, while antibody-mediated reactions tend to be more immediate. A well-known reason for immediate reactions is the presence of antigen specific IgE antibodies attached to the surface of mast cells and basophil granulocytes. After cross-linking of IgE antibodies on the surface of these cells, a degranulation process follows, resulting in production of histamine and many other mediator substances. Other stimuli can also cause degranulation such as the degree of ionization, osmolality, and temperature of the injected solution. Some drugs such as fluoroquinolones are known to cause histamine release without the presence of specific IgE, via non-IgE-dependent activation routes of the mast cell (McNeil, 2015).

Compared to reactions to iodine-based CM, reactions to gadolinium-based CA are more frequently IgE-mediated, and thus true allergic reactions (Clement, 2018).

Remember: Not all symptoms experienced by patients in the hour after contrast agent injections are adverse reactions to the contrast agent. Patient anxiety may cause symptoms after contrast agent administration, known as the Lalli effect (Lalli, 1974).

Clinical features and risk factors

The same acute adverse reactions are seen after intravascular administration of iodine-based contrast media and after gadolinium-based contrast agents or ultrasound contrast agents.

The term *adverse drug reaction (ADR)* is wider than hypersensitivity reactions, and includes several chemotoxic effects of CM injection (ADR type A), such as a feeling of warmth, dry mouth, or mild pain during injection, etc. Therefore, incidence figures between studies on hypersensitivity reactions and studies on ADR (for example post-marketing surveillance studies) can vary.

In Radiology, hypersensitivity reactions are usually discriminated into mild, moderate, or severe reactions as outlined below. It must be realized that in Allergology other classifications are used, discriminating reactions as allergic, non-allergic, or type A adverse reactions (see Figure 1 Schematic of adverse drug reaction types and Torres, 2021).

The chance that a reaction can be classified as allergic is lower when the reaction is mild or moderate. It is important to note that re-exposure to CM after an initial mild reaction never causes a moderate or severe reaction (Lee, 2017; Davenport, 2009).

Mild reactions include *allergy-like* hypersensitivity reactions such as scattered urticaria/pruritus, limited cutaneous oedema, itchy/scratchy throat, nasal congestion, and sneezing/conjunctivitis/ rhinorrhoea. This category also includes *physiologic* reactions such as limited nausea/vomiting, transient flushing/warmth/chills, headache/dizziness/anxiety, altered taste, mild hypertension or spontaneously resolving vasovagal reactions (ACR, 2022; ESUR, 2018; Wang, 2008).

Moderate reactions include *allergy-like* reactions such as diffuse urticaria/pruritus, diffuse erythema with stable vital signs, facial oedema without dyspnoea, throat tightness/hoarseness without dyspnoea, and mild wheezing/bronchospasm. *Physiologic* reactions include protracted nausea/vomitus, hypertensive urgency, isolated chest pain, and vasovagal reactions responsive to treatment (ACR, 2022; ESUR, 2018; Wang, 2008).

Severe reactions include *allergy-like* reactions such as diffuse erythema with hypotension, diffuse/facial oedema with dyspnoea, laryngeal oedema with stridor, and severe wheezing/ bronchospasm with hypoxia, and generalized anaphylactic reaction/shock. Severe *physiologic* reactions include treatment-resistant vasovagal reactions, arrhythmia, hypertensive emergencies, and convulsions/seizures. Also, to this category belong pulmonary oedema and cardiopulmonary arrest (ACR, 2022; ESUR, 2018; Wang, 2008).

Risk factors

Risk factor analysis is often done by retrospective observational studies without control groups (see also chapter chapter 3.5.3 Risk Factors for Hypersensitivity Reactions to Contrast Media). Risk factors for hypersensitivity are not fully established. Additional risk factors for immediate HSR that are common to allergic drug reactions include poorly controlled bronchial asthma, concomitant medications (e.g., ACE inhibitors, ß-blockers, and proton pump inhibitors), rapid administration of the drug, mastocytosis, autoimmune diseases, and viral infections (Rosado Ingelmo, 2016).
In Radiology literature, the most consistently reported risk factors for hypersensitivity reactions to CM are (ACR, 2022):
1. A prior hypersensitivity reaction to contrast media.
2. A history of allergy, particularly multiple severe allergies (atopy).
3. A history of asthma requiring treatment.

Female gender could not be substantiated as an independent risk factor for hypersensitivity reactions, but age may be relevant (Endrikat, 2022).

**Incidence of acute hypersensitivity reactions**

Incidence after iodine-based contrast media

The incidence is highest after iodine-based contrast media and lowest after ultrasound contrast agents. The incidence of acute adverse reactions has declined considerably after the introduction of low-osmolar and iso-osmolar iodine-based contrast media (ACR, 2022; ESUR, 2018).

In the early days of low-osmolar media, the classic Japanese study (Katayama, 1990) reported relatively high adverse drug reaction rates after nonionic CM of up to 3,1%, with severe and very severe reactions occurring in 0,44%. In contrast, more recent studies with large patient cohorts focusing more specifically on hypersensitivity (allergic-like) reactions have shown considerably lower incidence rates of 0,15 to 0,69% with severe reactions occurring in 0,005 to 0,013% (Hunt, 2009; Mortele, 2005; Wang, 2008).

Hypersensitivity reactions after non-vascular CM administration (either oral, rectal, intraductal, intravesical or intra-articular) are rare (see also the overview in Safe Use of Contrast Media, part 2). Such reactions occur slower, and the incidence is much lower than after intravascular administration and will be influenced by the integrity and condition of the wall of the cavity into which the contrast agent is administered (for example inflamed mucosa may lead to leakage into the intravascular compartment). Nevertheless, severe reactions can occur, even with non-vascular CM administration (Davis, 2015).

Incidence using specific iodinated contrast media

Large post-marketing surveillance studies of iobitridol and iodixanol have shown acute adverse events of 0,58-0,59% with severe events in 0,004 to 0,010% (Maurer, 2011; Zhang, 2014). A third study using iopromide is more difficult to compare due to different definitions, and had higher rates of 2,49% and 0,034%, respectively (Palkowitsch, 2014). It must be noted that physiologic reactions (feeling of warmth, metallic taste) make up a considerable part of these events.
More recently, the hypersensitivity reaction rate after iopromide was 0,74% in adults and 0,38% in elderly (Endrikat, 2022). In the same study population, the hypersensitivity reaction rate was 0.7% after intravenous administration vs. 0.2% after intra-arterial administration (Endrikat, 2020).

In addition, several retrospective observational studies have looked at differences in acute hypersensitivity rates among iodine-based CM. Although imperfect, these studies indicate a somewhat higher rate for iopromide and iomeprol compared to other CM (An, 2019; Gomi, 2010; Kim, 2017; Seong, 2014). It remains controversial whether iobitridol has a lower percentage, as indicated in one study (Kim, 2017).

Incidence after gadolinium-based contrast agents

Recent studies in large adult patient cohorts focusing on hypersensitivity (allergic-like) reactions have shown low incidence rates of 0,06-0,17% with severe reactions occurring in 0,003-0,006% (Aran, 2015; Behzadi, 2018; Dillman, 2007; Prince, 2011). More recent studies showed overall rates of 0,15-0,40%. For severe reactions rates were 0,002-0,004% in general populations and 0,033% in a population undergoing cardiac MRI (Ahn, 2022; McDonald, 2019; Uhlig, 2019).

In a large meta-analysis, the overall rate was 92 per 100,000 gadolinium-based contrast agent (GBCA) injections (0,09%) with severe reactions occurring in 5,2 per 100,000 injections (0,005%). It was shown that the type of GBCA is of influence on the number of reactions. Linear nonionic GBCA had an incidence of 15 per

100,000 and linear ionic GBCA of 52 per 100,000. However, these GBCA are no longer available in Europe. The macrocyclic GBCA had slightly higher rates, macrocyclic ionic GBCA 90 per 100,000 and macrocyclic nonionic GBCA 160 per 100,000. The highest rate was for linear ionic GBCA with protein-binding, 170 per 100,000 injections (Behzadi, 2018).

Comparing specific GBCA, in one study more hypersensitivity reactions occurred after gadobenate and gadobutrol compared with gadodiamide or gadoterate injection (McDonald, 2019), while in another study most acute reactions occurred with gadoteridol and most delayed reactions with gadoterate (Ahn, 2022).

**Breakthrough, protracted and biphasic hypersensitivity reactions**

So-called “breakthrough” hypersensitivity reactions are recurring reactions despite premedication with corticosteroids and H1-antihistamines. The occurrence in published series is variable, 2 to 17%. These reactions are most often of similar severity as the original (culprit) reaction for which premedication was prescribed. Breakthrough reactions can be severe in incidental cases. Unfortunately, no data on the number of IgE-mediated reactions are available (Davenport, 2009; Mervak, 2015).

While most hypersensitivity reactions to CM are uniphasic, other patterns may also occur. A *protracted* reaction is defined as a reaction lasting > 5h in which symptoms incompletely resolve. This pattern is rare following CM, occurring in only 4% of anaphylactic (severe) reactions and may be predicted by a low responsiveness to initial adrenaline therapy (Kim, 2018).

A *biphasic* reaction is defined as a reaction recurring 0 to 72h after an initial hypersensitivity reaction. The median time for start of the second reaction is 8 to 12h after the first reaction. This pattern is also rare, occurring in 10% of anaphylactic (severe) reactions (Rohacek, 2014). Usually, the second reaction is of similar severity or milder than the initial reaction. Predictors for biphasic anaphylaxis are severe initial symptoms requiring adrenaline redosing or a long (> 40 min) duration of the initial reaction. An observation time of 6-12h after the initial anaphylactic reaction has resolved is practical (Lee, 2016; Kim, 2018 and 2019). The use of corticosteroids in this setting is controversial and is not recommended (Gabrielli 2019; Lee, 2016; Simons, 2015).

For ultrasound contrast agents the risk is low, but no large series have been published to date. Most adverse reactions are cardiovascular, and the incidence of hypersensitivity reactions is 0,009% with severe reactions occurring in 0,004% (Khawaja, 2010).

**Classification**

Historically, hypersensitivity reactions to CM have been graded as mild, moderate, or severe. This radiological classification shows overlap with other used classifications, such as the World Allergy Organisation (WAO) classification (Johansson, 2004) and modifications of the Ring - Messmer classification of allergic reactions (Ring, 1977; Table 1 *Severity grading of anaphylactic reactions* (modified Ring and Messmer)).

**Table 1 Severity grading of anaphylactic reactions (modified Ring and Messmer)**

| Grade | Skin | Abdomen | Airways | Cardiovascular |
|---|---|---|---|---|
| I | Itch<br>Flush<br>Urticaria<br>Angioedema | - | - | - |
| II | Itch<br>Flush<br>Urticaria<br>Angioedema | Nausea<br>Cramps | Rhinorrhoea<br>Hoarseness<br>Dyspnoea | Tachycardia (> 20 bpm)<br>Hypertension (>20 mm Hg)<br>Arrhythmia |
| III | Itch<br>Flush<br>Urticaria<br>Angioedema | Vomiting<br>Defecation | Laryngeal oedema<br>Bronchospasm<br>Cyanosis | Shock |
| IV | Itch<br>Flush<br>Urticaria<br>Angioedema | Vomiting<br>Defecation | Respiratory arrest | Cardiac arrest |

*Classification according to the most severe symptom, no symptom is mandatory*

A practical summary classification of acute hypersensitivity reactions to contrast media for radiological practices may be (free after ACR, 2022; ESUR, 2018):

**Mild:** Itching, sneezing, flushing, conjunctivitis, rhinorrhoea, epiphora, nausea, short-duration, or incidental vomiting, altered taste, limited (localized) scattered urticaria.
**Moderate:** Generalized or extensive urticaria, diffuse erythema without hypotension, facial or angioedema without dyspnoea, mild wheezing/bronchospasm, protracted vomiting, mild isolated hypotension.
**Severe:** Severe wheezing/bronchospasm, profound hypotension, pulmonary oedema, generalized anaphylactic reaction, seizures/convulsions, respiratory arrest, and cardiac arrest.

It is important to note that re-exposure to CM after an initial mild reaction never causes a moderate or severe reaction (Lee, 2017; Davenport, 2009). In addition to this, the risk of an IgE-mediated allergic reaction (and thus the risk of severe reactions in case of re-exposure) is low in moderate reactions without cutaneous symptoms. Therefore, in the classification most used in allergology only reactions with cutaneous symptoms (urticaria or angioedema) are classified as allergic-like (Torres, 2021).

**Nonimmediate (late, delayed) hypersensitivity reactions to Contrast Media**
Clinical features
A nonimmediate hypersensitivity reaction (NIHR) is a delayed hypersensitivity reaction > 1h after contrast administration (usually > 24h). NIHR usually presents as a maculopapular exanthema (MPE): skin rash consisting of patches (maculae) and nodules (papulae) spread over body and extremities. It normally heals within days to weeks, and if treatment is required, topical or oral steroids can be applied.

Many patients show a variety of nonspecific symptoms, which include headache, nausea, dizziness, gastro-intestinal upset, mild fever, and arm pain (Bellin, 2011; Christiansen, 2000). When compared to control populations (Loh, 2010), skin rashes with erythema and swelling are the most frequent true nonimmediate hypersensitivity reactions. Most patients present with cutaneous symptoms like other drug-induced skin eruptions, usually in the form of a macular or maculopapular exanthema. The exanthema usually occurs 2 to 10 days after first exposure to ICM and 1 to 2 days after re-exposure to the same ICM. Most reactions are mild to moderate in severity, are usually self-limiting and resolve within 1 week (Bellin, 2011).

Discrimination should be made between mild-to-moderate NIHR and rare severe NIHR with danger signs, the so-called severe cutaneous adverse drug reactions (SCAR), such as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, toxic epidermal necrolysis (TEN), acute generalized exanthemic pustulosis (AGEP), and Stevens-Johnson syndrome (SJS) (Brockow, 2019; Soria, 2021).

**Pathophysiology**

There is evidence that drug-specific T-cells play an important role in nonimmediate hypersensitivity reactions. In skin reactions an infiltrate in the dermis consisting of activated CD4+ or CD8+ T-cells and eosinophils is usually found (Christiansen, 2000 and 2003; Schönmann, 2020).

*In vitro* studies have shown two different pathways of CM recognition which both require major histocompatibility complex (MHC) molecules for stimulation: a) direct binding of CM to the T-cell receptor or MHC molecule (p-i concept), and b) after uptake and processing by antigen-presenting cells and presented to T-cells via MHC-II molecules ((pro)hapten concept) (Keller, 2009).

The hapten-independent pathway could explain results of cross-reactivity analyses that revealed that CM-specific activated T-cell clones reacted to CM with shared structural elements.

It has been postulated that CM do not induce a primary immune response, but instead interact with receptors on activated memory T-cells raised against other foreign substances (non-allergic NIHR). Patients with nonimmediate hypersensitivity should not be at risk for an immediate hypersensitivity reaction (mediated by IgE or other mechanisms) upon re-exposure to CM.

**Risk factors**

Established risk factors for nonimmediate hypersensitivity reactions to iodine-based CM include a previous hypersensitivity reaction and IL-2 immunotherapy. Most CM-associated nonallergic NIHR are associated with iso-osmolar CM (ACR, 2022; Bellin, 2011; ESUR, 2018).

Patients with a history of nonimmediate hypersensitivity reactions to ICM are not at increased risk for immediate HSR to ICM as these reactions are mechanistically unrelated (Christiansen, 2003; Mazori, 2018).

**Incidence of nonimmediate hypersensitivity reactions**

The frequency of nonimmediate hypersensitivity reactions to CM varies greatly between studies and is believed to be between 1-3% of patients after iodine-based CM administration and only very rarely after gadolinium-based CA administration (Bellin, 2011; Christiansen, 2000).

Incidence using specific iodine-based CM

Nonimmediate skin reactions tend to be more common after iodixanol (Benin, 2011; Sutton, 2003). The incidence of nonimmediate hypersensitivity reactions is not significantly different for the other iodine-based low-osmolar CM (Bellin, 2011).

## Cross-reactivity between contrast media

*Cross-reactivity between iodine-based CM*

Most of the current cross-reactivity data come from skin testing. Cross-reactivity in late hypersensitivity reactions is probably caused by the presence of CM-specific T-cells, some of which may show a broad cross-reactivity pattern. There may be a link between the chemical structure of iodine-based CM and the pattern of cross-reactivity, but results are inconsistent.

Several studies have shown considerable cross-reactivity between different iodine-based CM, but specific data on immediate versus nonimmediate hypersensitivity reactions are lacking until now. In the larger studies, most cross-reactivity has been seen between the nonionic dimer iodixanol and its monomer iohexol, with relatively fewer positive skin reactions with iobitridol (Clement, 2018; Hasdenteufel, 2011; Lerondeau, 2016; Yoon, 2015).

Based on cross-reactivity patterns iodine-based CM may be divided in three groups, with relatively high intra-group cross-reactivity but less intergroup cross-reactivity (Lerondeau, 2016). Based on additional data, it seems reasonable to add iopromide to group A as well and possibly remove ioxithalamate and iopamidol (Schrijvers, 2018).

Table 2 Cross-reactivity grouping of iodine-based CM (Lerondeau, 2016) may be helpful for selecting an alternative agent for imaging studies.

**Table 2 Cross-reactivity grouping of iodine-based CM (Lerondeau, 2016)**

| Group A | Group B | Group C |
|---|---|---|
| Ioxithalamate (Telebrix) | Iobitridol (Xenetix) | Amidotrizoate (Gastrografin) |
| Iopamidol (Iopamiro) | Ioxaglate (Hexabrix) | |
| Iodixanol (Visipaque) | | |
| Iohexol (Omnipaque) | | |
| Ioversol (Optiray) | | |
| Iomeprol (Iomeron) | | |
| Iopromide (Ultravist) | | |

*Note: Iopamidol and Ioxaglate are no longer available on the market in The Netherlands*

Cross-reactivity between gadolinium-based CM

Information on cross-reactivity between GBCA is limited to case reports. Skin testing and provocation tests in such cases have shown that cross-reactivity among macrocyclic GBCA may be more extensive than among linear GBCA (Gallardo Higueras, 2021; Grüber, 2021).

Cross-reactivity between iodine-based and gadolinium-based CM

A recent study examined the risk of reactions to both iodine-based CM and gadolinium-based CA in the same patient in a large patient cohort. The incidence of primary hypersensitivity reactions was 0,047% and the incidence of secondary reactions 0,024%. Nearly all reactions were mild, requiring no treatment. Therefore, cross-reactivity between iodine-based and gadolinium-based CM is an extremely rare event (Sodagari, 2018).

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## Verantwoording

Laatst beoordeeld : 28-11-2022

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

# Definities van bijwerkingen

## Definitions of Adverse Drug Reactions

*Disclaimer: This narrative supplement has been written by members of the Guideline Development Group so that non-specialized readers can follow the text more easily. It was not part of the actual guideline process with structured literature analyses.*

**Adverse drug reaction (ADR),** synonyms: Adverse reaction, Suspected adverse (drug) reaction, Adverse effect, Undesirable effect (CIOMS IX)
A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse, and medication errors (EMA, 2017).
The terms “adverse reaction” and “adverse effect” are interchangeable, except that an adverse effect is seen from the point of view of the drug, whereas an adverse reaction is seen from the point of view of the patient (Edwards, 2000).

**Toxic effect**
A toxic effect is an effect that occurs as an exaggeration of the desired therapeutic effect, and which is not common at normal doses. It occurs by the same mechanism as the therapeutic effect and is always dose related.

**Side effect**
A side effect is any effect that is not the main aim of a therapy. Side effect include effects that may be beneficial rather than harmful. A side effect may or may not occur through the pharmacological action for which the drug is being used.

**Unexpected adverse reaction**
An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drug

**Serious adverse effect**
Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening

- Cancers and congenital anomalies or birth defects should be regarded as serious
- Medical events that would be regarded as serious if they had not responded to acute treatment should also be considered serious
- The term ‘severe’ is often used to describe the intensity (severity) of a medical event, as in the grading ‘mild’, ‘moderate’, and ‘severe’; thus, a severe skin reaction need not be serious

**Adverse event/adverse experience**
Any untoward occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relation to the treatment

**Drug hypersensitivity reaction (DHR)**
Drug hypersensitivity reactions (DHRs) are adverse effects of drugs that clinically resemble allergic reactions ('pseudo-allergic'). DHR includes adverse reactions that are immune or nonimmune mediated. For general communication, when an allergic drug reaction is suspected DHR is the preferred term, because true drug allergy and nonallergic DHR may be difficult to differentiate based on the clinical presentation alone, especially in cases of acute severe DHR.
Clinically, DHRs are commonly classified as immediate or nonimmediate/delayed depending on their onset during treatment. The discrimination between immediate and nonimmediate DHR has its limitations because other factors such as the route of administration, the role of drug metabolites, and the presence of co-factors or co-prescribed drugs may accelerate or slow down the onset or progression of a reaction. Although artificial, this classification into immediate and nonimmediate DHR is very important in clinical practice for workup planning.

**Non-immune drug hypersensitivity reaction**
Nonimmune hypersensitivity drug reactions are all adverse drug reactions whose symptomatology suggests an allergy but for which the immunologic nature of the reaction cannot be proved.
Nonimmune drug hypersensitivity reactions assume most of the criteria listed under drug allergy. Numerous nonimmune hypersensitivity reactions occur and are caused by multiple aetiologies. Examples include:

- Include nonspecific histamine release (opiates, radiocontrast media, and vancomycin),
- An accumulation of bradykinin (angiotensin-converting enzyme inhibitors),
- Complement activation (radiocontrast media, protamine),
- An activation of leukotriene synthesis (aspirin and nonsteroidal anti-inflammatory drugs),
- Bronchospasm (by liberation of sulphur dioxide during treatments containing sulphites or by blockage of the b-adrenergic receptors, even when the drug is administered through the eyes).
- Nonimmediate drug hypersensitivity like reaction due to pharmacological interaction with immune receptor. P-i concept reactions are associated with specific HLA types.

**Immediate drug hypersensitivity reaction (IHR)**
Immediate DHRs are possibly induced by an IgE-mediated mechanism and occur within 1–6 h after the last drug administration. Typically, they occur within the first hour following the first administration of a new course of treatment.
Immediate DHRs usually present with urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhoea), or anaphylaxis, which can lead to cardiovascular collapse (anaphylactic shock)

**Non-immediate drug hypersensitivity reaction (NIHR)**
Nonimmediate DHRs may occur any time as from 1 h after the initial drug administration. They commonly occur after many days of treatment and are often associated with a delayed T-cell-dependent type of allergic mechanism.

Nonimmediate DHRs often affect the skin with variable cutaneous symptoms such as late occurring or delayed urticaria, maculopapular eruptions, fixed drug eruptions (FDE), vasculitis, blistering diseases (such as TEN, SJS, and generalized bullous fixed drug eruptions), HSS, acute generalized exanthematous pustulosis (AGEP), and symmetrical drug-related intertriginous and flexural exanthemas (SDRIFE). Internal organs can be affected either alone or with cutaneous symptoms (HSS/DRESS/DiHS, vasculitis, SJS/TEN) and include hepatitis, renal failure, pneumonitis, anaemia, neutropenia, and thrombocytopenia.

**Drug allergy**
A drug allergy is always associated with an immune mechanism for which evidence can be shown of drug-specific antibodies or activated T lymphocytes. Drugs can induce all the types of immunologic reactions described by Gell and Coombs
A drug allergy is characterized by the following criteria:

- The reaction is not an expected pharmacologic effect.
- A period of sensitization precedes the reaction.
- The reaction may occur at a dose much lower than that required for a pharmacologic effect.
- The clinical symptoms are characteristic of an allergic reaction.
- Resolution occurs within an expected interval, usually days, after discontinuation of the offending agent.
- Chemical cross-reactivity may occur

**Classification of Adverse Drug Reactions**

**Type A adverse drug reaction**
Type A (augmented) reactions result from an exaggeration of a drug's normal pharmacological actions when given at the usual therapeutic dose and are normally dose dependent. Examples include respiratory depression with opioids or bleeding with warfarin. Type A reactions also include those that are not directly related to the desired pharmacological action of the drug, for example dry mouth that is associated with tricyclic antidepressants

**Type B adverse drug reaction**
Type B (bizarre) reactions are novel responses that are not expected from the known pharmacological actions of the drug. These are less common, and so may only be discovered for the first time after a drug has already been made available for general use.
Examples include anaphylaxis with penicillin or skin rashes with antibiotics.
Type B ADR include adverse reactions that are dose-independent, unpredictable, noxious, and unintended response to a drug taken at a dose normally used in humans. However, some dose dependence has been shown repeatedly in DHRs (e.g., for nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptic drugs) and some are predictable due to the disease state (e.g., human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS), Epstein–Barr virus (EBV) infection) or a similar previous reaction to the same drug or drug class. Some are associated with specific HLA types

**Type C adverse drug reaction**
Type C ('continuing') reactions persist for a relatively long time. Examples are osteonecrosis of the jaw with

bisphosphonates, Hypothalamic-pituitary-adrenal axis suppression by corticosteroids

**Type D adverse drug reaction**
Type D ('delayed') reactions become apparent sometime after the use of a drug. The timing of these may make them more difficult to detect. An example is leucopoenia, which can occur up to six weeks after a dose of lomustine. Teratogenic (e.g., vaginal adenocarcinoma with diethylstilbesterol) and carcinogenic reactions can also be type D reactions.

**Type E adverse drug reaction**
Type E ('end-of-use') reactions are associated with the withdrawal of a drug. An example is insomnia, anxiety and perceptual disturbances following the withdrawal of benzodiazepines.

**Type F adverse drug reaction**
Type F (failure) reactions are the result of unexpected failure of therapy. An example is inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers (interaction).

**Causality assessment of suspected adverse drug reactions**

**Certain**
• A clinical event, including a laboratory test abnormality, which occurs in a plausible time relation to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals
• The response to withdrawal of the drug (de-challenge) should be clinically plausible
• The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary

**Probable/likely**
• A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge)
• Rechallenge information is not required to fulfil this definition

**Possible**
• A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals
• Information on drug withdrawal may be lacking or unclear

**Unlikely**
• A clinical event, including a laboratory test abnormality, with a temporal relation to administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations

**Conditional/unclassified**

• A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment, or the additional data are being examined

Not assessable/unclassifiable
• A report suggesting an adverse reaction that cannot be judged, because information is insufficient or contradictory and cannot be supplemented or verified

### Literature For Further Reading

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## Verantwoording

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# Behandeling van acute hypersensitiviteitsreacties na CM

## Uitgangsvraag

Wat is de optimale behandeling van acute hypersensitiviteitsreacties na contrastmiddel (CM)-toediening?

## Aanbeveling

### Voorbereiding:

- Zorg ervoor dat de medicatie (als minimum vereiste: adrenaline, salbutamol, H1-antihistaminicum (clemastine) IV en corticosteroid IV (bijvoorbeeld prednisolon)), uitrusting en protocol voor de behandeling van een acute hypersensitiviteitsreactie gereed liggen in elke kamer waar CM worden toegediend.
- Houd je aan lokale protocollen voor bereikbaarheid van een reanimatie en een spoed interventie team (SIT).
- Houd elke patiënt met een acute hypersensitiviteitsreactie na toediening van CM in een medische omgeving gedurende minstens 30 minuten na injectie van CM. Matige en ernstige reacties behoeven een langere observatietijd.

### Acute behandeling, algemene principes:

- Check en stabiliseer de patiënt volgens de ABCDE-methode.
- Stop met toediening van CM en vervang infuus door een kristalloïd.
- Dyspneu of stridor: laat patiënt rechtop zitten.
- Hypotensie: houd patiënt in liggende positie, leg de benen hoger.
- Overweeg het bepalen van serum tryptase (zie aanbevelingen in *module 3.5.1 In vitro testen bij patiënten met hypersensitiviteitsreacties na CM*).
- Vermeld acute hypersensitiviteitsreacties in de allergieregistratie van het Elektronisch Patiënten Dossier (zie *hoofdstuk Organisatie van zorg Hypersensitiviteitsreacties*).

*N.B: Na toediening van clemastine kan het reactievermogen van de patiënt sterk verminderd zijn. Patiënt wordt afgeraden gedurende die tijd een voertuig te besturen of een machine te bedienen. Patiënt is strafbaar en vaak niet verzekerd bij eventueel ongeluk/schade.*

### Ernstige reacties:
### Cardiaal of respiratoir arrest:

- Start cardiopulmonale reanimatie.
- Bel het reanimatie team.

### Anafylactische reactie of stridor:

- Bel het Spoed Interventie Team (SIT-team).
- Geef zuurstof 10 tot 15L/min via een non-rebreathing masker.
- Geef 0.5mg adrenaline IM in laterale bovenste deel van het dijbeen.

- Geef bolus van een kristalloïd 500ml IV in 10 minuten, herhaal indien nodig.
- Overweeg verneveling met salbutamol 5mg of budesonide 2mg voor stridor.
- Geef clemastine 2mg IV, herhaal indien nodig.
- Overweeg toevoegen corticosteroid (b.v. prednisolon 50mg IV*)

* Of equivalente dosis van een ander corticosteroïd
50 mg prednisolon is equivalent aan:

- 40 mg methylprednisolone.
- 8mg dexamethasone.
- 200mg hydrocortisone.

* Overweeg toevoegen van corticosteroïden voor preventie van geprotraheerde of bifasische anafylactische reacties als de initiële symptomen ernstig zijn.

**Matig-ernstige reacties:**
Overweeg om patiënt te verplaatsen naar een afdeling met faciliteiten voor het monitoren van vitale functies.

**Geïsoleerd bronchospasme:**

- Salbutamol 2.5 tot 5mg verneveling in zuurstof door middel van een gezichtsmasker 10 tot 15 L/min (verneveling is makkelijker om toe te dienen en meer effectief dan dosis aerosol).
- Bij milde reacties mogen astmapatiënten de eigen salbutamoldosis aerosol gebruiken.
- Indien klachten toenemen geef adrenaline 0.5mg IM en neem contact op met het spoed-interventie-team.

**Geïsoleerd gezichtsoedeem zonder stridor:**

- Geef zuurstof 10 tot 15L/min via een non-rebreathing masker.
- Geef clemastine 2mg IV.
- Indien oedeem ernstig is of dichtbij luchtwegen is gelokaliseerd of indien er stridor ontstaat: behandel als anafylaxie.

**Geïsoleerde urticaria/diffuse erytheem:**

- Geef clemastine 2mg IV.
- Indien vergezeld van hypotensie: behandel als anafylaxie.

**Geïsoleerde hypotensie:**

- Geef bolus van kristalloïd 500ml IV, herhaal indien nodig.
- Indien vergezeld van bradycardie, overweeg atropine 0.5mg IV.
- Indien vergezeld door andere symptomen behandel als anafylaxie.

**Milde reacties**

**Algemeen:**

- Milde reacties behoeven soms enkel geruststelling.
- Observeer vitale functies totdat symptomen voorbij zijn.
- Verwijder iv toegang niet tijdens observatie.

**Overweeg:**

- Voorschrijven van een niet-sederend H1-antihistaminicum, bijvoorbeeld desloratidine 5mg PO (eenmaal daags) voor milde hypersensitiviteitsreacties.
- Ondansetron 4mg iv voor persistent overgeven.

## Overwegingen

As there are no comparative studies investigating the research question, the recommendations in this national guideline are based mainly on results of observational studies and reviews (for example Cohan, 1996; Bang, 2013; Morzycki, 2017; Boyd, 2017) and of the recommendations of the American College of Radiology 2018 (Manual on Contrast Media v10.3) (ACR, 2018), the European Society of Urogenital Radiology 2018 (electronic v10) (ESUR, 2018), the International Consensus On Drug Allergy 2014 (Demoly, 2014), the World Allergy Organisation (WAO) Anaphylaxis Guidelines 2011, update 2015 (Simons, 2015), the European Association for Allergy and Clinical Immunology (EAACI) Guidelines 2014 (Moraro, 2014), and adapted to the Dutch situation (Het Acute Boekje, NIV 2017).

Because of the diminished frequency of acute adverse reactions to contrast media, there are now fewer opportunities for physicians to recognize and appropriately treat such adverse reactions. Reactions vary from very mild itching to anaphylactic shock. These reactions are often unpredictable; they can happen to people who have not been exposed to contrast media in the past. A mild reaction may be self-limited but can also develop quickly into a severe reaction. When a hypersensitivity reaction to a contrast medium occurs, there may be insufficient time or opportunity to study the treatment protocols and medication doses. It is therefore important for personnel to be prepared for any adverse reaction, to have clear treatment guidelines, and to have access to a rapid response team in case of an emergency. (Segal, 2011).

Because of this diminished frequency and lack of experience in treatment, major guidelines recommend to restricting adrenaline injection in the hands of non-experienced users to intramuscular administration route only.

*Risk factors*
Patients with a history of previous moderate or severe acute hypersensitivity reaction to an iodine-based contrast medium or gadolinium-based or ultrasound contrast agent, asthma requiring medical treatment and atopy requiring medical treatment are at increased risk (ESUR 2018; ACR 2018).

*Prevention*
Use a low-osmolar or iso-osmolar non-ionic iodine-based contrast medium. In patients at risk consider an alternative test not requiring a contrast agent of similar class.

For previous contrast agent reactors: use a different contrast medium/agent, preferably after consultation with a specialist in drug allergy

The radiology department should be prepared for an acute reaction. This requires regular and optimized training of personnel. See Chapter: Organisation of healthcare.

Note:
Instead of adrenaline 1:1,000 ampules for IM administration each department may also opt for selecting the (more expensive) adrenaline 1:1,000 auto-injectors, for example EpiPen (Asch 2017).

## Onderbouwing

### Achtergrond

Acute hypersensitivity reactions often create stress and confusion and appropriate training and clear protocols are advisable. In addition, depending on the location where a patient suffers an acute hypersensitivity reaction to contrast media, the available expertise of the personnel that cares for such a patient may differ. Similarly, the availability of equipment and drugs to treat a (possible serious) hypersensitivity (or anaphylactic) reaction will be different. In a radiology or cardiology department the possibilities are different (and usually more limited) than in a department of emergency medicine or on a hospital ward. In addition, different treatments will have variable modes of action. What is the most appropriate management of a patient with an acute hypersensitivity reaction to contrast media?

### Samenvatting literatuur

Not applicable. There were no studies investigating the research question. The non-comparative studies are briefly described in the evidence table below.

### Zoeken en selecteren

To answer the clinical question a systematic literature analysis was performed.

**P (Patient)** Patients with acute hypersensitivity reaction after contrast media administration.
**I (Intervention)** Treatment, antihistamines, corticosteroids, epinephrine, adrenalin, dopamine, norepinephrine, noradrenalin, histamine H1 antagonists, histamine H2 antagonists, H1 antihistamines, H2 antihistamines, adrenergic beta-2 receptor agonists, glucocorticoids, management/treatment of hypersensitivity reactions/allergic reactions after contrast media, antihistamines, volume resuscitation, bronchodilators.
**C (Comparison)** Conservative treatment or comparison of interventions mentioned above.
**O (Outcomes)** Duration of acute reaction, severity of complaints, morbidity, mortality, costs, hospitalization in an IC-unit, length of stay.

Relevant outcome measures
The working group considered morbidity, mortality, and hospitalization in an IC-unit, critical outcome measures for the decision-making process, and duration of acute reaction, length of stay and costs important outcomes for the decision-making process.

Methods

The databases Medline (OVID) and Embase were searched from 1ˢ of January 1985 to 28th of December 2017 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS).

Search terms are shown under the Tab "Literature Search". The literature search procured 328 hits: 20 SR, 64 RCTs and 224 OBS. Based on title and abstract a total of 47 studies were selected. After examination of full text all studies were excluded, and no studies definitely included in the literature summary.

4 studies describing treatment effects of acute adverse reactions were found. Although these studies did not fulfil the search criteria, a short description is included in the literature summary, due to lack of other evidence. Since no control groups were available, no evidence tables or risk of bias tables or conclusions of these studies are included.

## Verantwoording

Laatst beoordeeld : 24-06-2020

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

## Referenties

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# Behandeling van late hypersensitiviteitsreacties na CM

## Uitgangsvraag

Wat is de optimale behandeling van late hypersensitiviteitsreacties na contrastmiddel-(CM)-toediening?

## Aanbeveling

Waarschuw patiënten die eerder een hypersensitiviteitsreactie hebben gehad na CM, dat een late hypersensitiviteitsreactie mogelijk is, meestal een huidreactie.

Patiënten moeten contact opnemen met hun huisarts als zij een late hypersensitiviteitsreactie hebben na CM-toediening.

Overweeg om de afdeling Radiologie waar het CM werd toegediend te informeren over het optreden en de symptomen van een late hypersensitiviteitsreactie na CM toediening.

Wanneer de symptomen van een late hypersensitiviteitsreactie mild zijn is afwachten te verdedigen.

Behandel late hypersensitiviteitsreacties naar gelang de symptomen.
Overweeg behandeling van huidreacties met orale of topicale corticosteroïden.

Wanneer ernstige symptomen ontstaan, zoals gegeneraliseerde pustulosis of pijnlijke cutane blaren, verwijs dan de patiënt naar een dermatoloog.

## Overwegingen

There are no solid data on different management strategies of late hypersensitivity reactions to CM, especially no studies with a control group.

In many patients there are nonspecific symptoms, such as headache, nausea, dizziness, gastro-intestinal upset, mild fever and arm pain (Bellin, 2011; Christiansen, 2000; Egbert, 2014). Skin rashes with erythema and swelling and headache are the most frequent true late hypersensitivity reactions or symptoms (Ioh, 2010). Most rashes are macular or maculopapular exanthemas, which usually occurs 2-10 days after first exposure to CM and 1 to 2 days after re-exposure to the same CM. Most reactions are mild to moderate in severity, are usually self-limiting and resolve within 1 week.

Treatment is symptomatic, based on the type of reaction presented. More than 90% of the late hypersensitivity reactions involve the skin only. Usually oral antihistamines and topical corticosteroid crèmes or emollients treat these late skin reactions.. Antipyretics may be given for fever, and anti-emetics for nausea or GI symptoms.

Very rarely the patient may develop a severe reaction with generalized pustulosis or blistering of the skin, for which specialized dermatology care needs to be sought (Egbert, 2014).

It seems therefore to be rational to follow the recommendations from the ESUR v10 guideline (Bellin, 2011; ESUR, 2018) and/or the ACR Manual on Contrast Media v10.3 (ACR 2018)

## Onderbouwing

## Achtergrond

Late (non-immediate) adverse reactions are heterogeneous. Because of the self-limiting character of most cutaneous adverse reactions to CM, the traditional mainstay of treatments follows that of cutaneous adverse reactions to other drugs: withdrawal of the drug and preventative measures for reuse of them, combined with symptomatic treatment.

Severe cutaneous reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS) may warrant specific therapeutic interventions by a dermatologist.

## Samenvatting literatuur

Not applicable. There were no studies investigating the research question.

## Zoeken en selecteren

To answer the clinical question a systematic literature analysis was performed.

**P** (Patients): Patients with late hypersensitivity reaction after contrast media administration.
**I** (Intervention): Diagnosis, treatment, management, steroid, cyclosporine, topical, emollients.
**C** (Comparison): Conservative treatment or comparison of interventions above.
**O** (Outcomes): Recovery, course, outcome, sequels, mortality, morbidity hospitalization.

Relevant outcome measures
The working group considered mortality and recovery critical outcome measures for the decision making process and course, sequel, morbidity and hospitalisation important outcomes for the decision making process.

Methods
The databases Medline (OVID), Embase and the Cochrane Library were searched from 1st of January 1985 to 3th of January 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). Search terms are shown under the Tab “Literature Search”. The literature search procured 480 hits: 11 SR, 72 RCTs and 336 OBS. Based on title and abstract a total of 12 studies were selected. After examination of full text all studies were excluded and 0 studies definitely included in the literature summary.

## Verantwoording

Laatst beoordeeld : 24-06-2020

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

## Referenties

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# Follow up strategieën na hypersensitiviteitsreacties na CM

This chapter is an update of the modules about hypersensitivity reactions in the earlier guidelineSafe Use of Contrast Media part 2.

Contents of chapter 3.5:

- Introduction to Hypersensitivity Reactions to Contrast Media (update of guideline part 2)
- Supplement Definitions of Adverse Drug Reactions (update of guideline part 2)
- Module 3.5.1 In Vitro Tests in Patients with Hypersensitivity Reactions to Contrast Media (update of guideline part 2)
- Module 3.5.2 Diagnostic Value of Skin Testing for Hypersensitivity Reactions to Contrast Media (update of guideline part 2)
- Module 3.5.3 Risk Factors of Hypersensitivity Reactions to Contrast Media (update of guideline part 2)
- Module 3.5.4 Prophylactic Measures for Prevention of Recurrent Hypersensitivity Reactions to Contrast Media (update of guideline part 2)
- Module 3.5.5 Hypersensitivity reactions after non-vascular CM (part 2)
- Appendix 1 Flow Charts (update of guideline part 2)
- Appendix 2 Contrast Media Hypersensitivity: The Lalli and Weber Effects
- Appendix 3 Allergology Services in The Netherlands

The increased use of contrast media (CM) may give rise to an increased absolute number of total hypersensitivity reactions (HSR). The relative number of immediate HSR has decreased since the introduction of nonionic, low-osmolar ICM, while the number of non-immediate HSR is on the rise, due to an increased use of iso-osmolar ICM (Rosado Ingelmo, 2016).

*Disclaimer: This narrative review has been written by members of the Guideline Development Group so that non-specialized readers can follow the Modules about Hypersensitivity more easily. It was not part of the actual guideline process with structured literature analyses.*

**Terminology and Definitions (see also Supplement)**
The following definitions and terminology are based on the standard terminology recommended by the World Allergy Organisation (Cordona, 2020; Demoly, 2014; Johansson, 2004). When dealing with CM, the term allergy should be avoided as much as possible.

*Hypersensitivity:* Objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus that is tolerated by normal subjects.

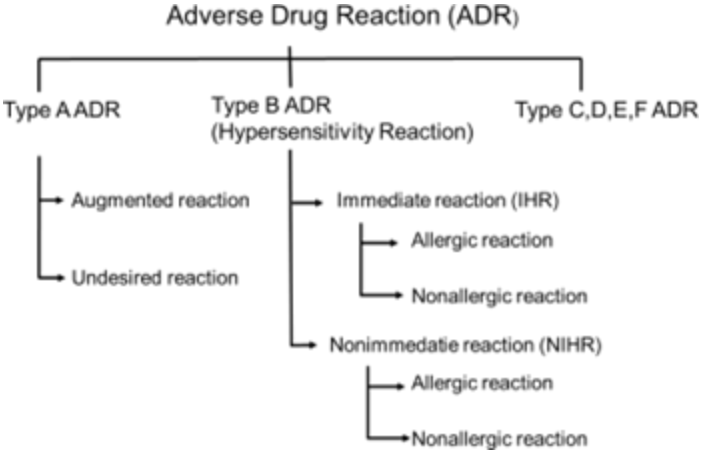
*Drug Hypersensitivity Reaction (DHR)*: adverse effects of drugs that clinically resemble allergic reactions ('pseudo-allergic'). These include adverse reactions that are immune or nonimmune mediated.

*Drug Allergy:* Hypersensitivity reactions that are associated with an immune mechanism for which evidence can be shown in the form of drug-specific antibodies or activated T lymphocytes.

*Immediate (acute, early) hypersensitivity reaction to contrast media:* an adverse reaction that occurs within 1 hour of contrast agent injection. Acute reactions can either be allergy- like (IgE-mediated or not) hypersensitivity reactions or chemotoxic responses.

*Non-immediate (delayed, late) hypersensitivity reaction to contrast media:* an adverse reaction that occurs between 1 hour and 1 week after contrast agent injection.

**Figure 1 Schematic of adverse drug reaction types**




*Adverse drug reaction (ADR):* a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man (WHO definition) (See Figure 1 Schematic of adverse drug reaction types)

ADR can be classified in multiple types, and for contrast media types A, B and D are most relevant. Type A (augmented) reactions result from an exaggeration of a drug's normal pharmacological actions when given at the usual therapeutic dose and are normally dose dependent. These include all physiologic reactions. Type B (bizarre) reactions are novel responses that are not expected from the known pharmacological actions of the drug. These are less common, and so may only be discovered for the first time after a drug has already been made available for general use. These include allergic or non-allergic hypersensitivity reactions. Type D, or 'delayed' reactions, become apparent sometime after the use of a medicine. The timing of these may make them more difficult to detect. These include Nephrogenic Systemic Fibrosis (NSF) or iodine-induced hyperthyroidism (Edwards, 2000).

*Anaphylaxis:* Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes (Cordona, 2020; WHO ICD-11 definition).

Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled (Cordona, 2020):
1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips- tongue-uvula)
And at least one of the following:

a. Respiratory compromise (e.g., dyspnoea, wheezing/bronchospasm, stridor, reduced PEF, hypoxemia)

b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
c. Severe gastrointestinal symptoms (e.g., severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens

2. Acute onset of hypotension[a] or bronchospasm[b] or laryngeal involvement[c] after exposure to a known or highly probable allergen[d] for that patient (minutes to several hours), even in the absence of typical skin involvement.

Note: a hypotension defined as a decrease in systolic BP greater than 30% from that person's baseline, or a systolic BP less than <90 mmHg. b. Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reactions in the absence of ingestion. c. Laryngeal symptoms include stridor, vocal changes, odynophagia. d. An allergen is a substance (usually a protein) capable of triggering an immune response that can result in an allergic reaction. Most allergens act through an IgE-mediated pathway, but some non-allergen triggers can act independent of IgE (for example, via direct activation of mast cells).

**Immediate hypersensitivity reactions to contrast media**

Pathophysiology

Hypersensitivity reactions to CM are poorly understood. Recent research suggests that hypersensitivity reactions to nonionic CM are a heterogeneous disease. It can develop from multiple mechanisms such as IgE-dependent, complement dependent, direct membrane effects of CM, and possibly other mechanisms that have not been identified yet (Zhai, 2017). When an allergic drug reaction is suspected, DHR is the preferred term, because true drug allergy and nonallergic DHR may be difficult to differentiate based on the clinical presentation alone, especially in cases of acute severe DHR (Demoly, 2014).

Allergy-like hypersensitivity reactions may or may not be truly IgE-mediated. In general, allergy can be either antibody- or cell-mediated. Cell-mediated reactions usually occur after one or several days, while antibody-mediated reactions tend to be more immediate. A well- known reason for immediate reactions is the presence of antigen specific IgE antibodies attached to the surface of mast cells and basophil granulocytes. After cross-linking of IgE antibodies on the surface of these cells, a degranulation process follows, resulting in production of histamine and many other mediator substances. Other stimuli can also cause degranulation such as the degree of ionization, osmolality, and temperature of the injected solution. Some drugs such as fluoroquinolones are known to cause histamine release without the presence of specific IgE, via non-IgE-dependent activation routes of the mast cell (McNeil, 2015).

Compared to reactions to iodine-based CM, reactions to gadolinium-based CA are more frequently IgE-mediated, and thus true allergic reactions (Clement, 2018).

Remember: Not all symptoms experienced by patients in the hour after contrast agent injections are adverse reactions to the contrast agent. Patient anxiety may cause symptoms after contrast agent administration, known as the Lalli effect (Lalli, 1974).

Clinical features and risk factors

The same acute adverse reactions are seen after intravascular administration of iodine- based contrast media and after gadolinium-based contrast agents or ultrasound contrast agents.

The term *adverse drug reaction (ADR)* is wider than hypersensitivity reactions, and includes several chemotoxic effects of CM injection (ADR type A), such as a feeling of warmth, dry mouth, or mild pain during injection, etc. Therefore, incidence figures between studies on hypersensitivity reactions and studies on ADR (for example post-marketing surveillance studies) can vary.

In Radiology, hypersensitivity reactions are usually discriminated into mild, moderate, or severe reactions as outlined below. It must be realized that in Allergology other classifications are used, discriminating reactions as allergic, non-allergic, or type A adverse reactions (see Figure 1 Schematic of adverse drug reaction types and Torres, 2021).

The chance that a reaction can be classified as allergic is lower when the reaction is mild or moderate. It is important to note that re-exposure to CM after an initial mild reaction never causes a moderate or severe reaction (Lee, 2017; Davenport, 2009).

Mild reactions include *allergy-like* hypersensitivity reactions such as scattered urticaria/pruritus, limited cutaneous oedema, itchy/scratchy throat, nasal congestion, and sneezing/conjunctivitis/ rhinorrhoea. This category also includes *physiologic* reactions such as limited nausea/vomiting, transient flushing/warmth/chills, headache/dizziness/anxiety, altered taste, mild hypertension or spontaneously resolving vasovagal reactions (ACR, 2022; ESUR, 2018; Wang, 2008).

Moderate reactions include *allergy-like* reactions such as diffuse urticaria/pruritus, diffuse erythema with stable vital signs, facial oedema without dyspnoea, throat tightness/hoarseness without dyspnoea, and mild wheezing/bronchospasm. *Physiologic* reactions include protracted nausea/vomitus, hypertensive urgency, isolated chest pain, and vasovagal reactions responsive to treatment (ACR, 2022; ESUR, 2018; Wang, 2008).

Severe reactions include *allergy-like* reactions such as diffuse erythema with hypotension, diffuse/facial oedema with dyspnoea, laryngeal oedema with stridor, and severe wheezing/ bronchospasm with hypoxia, and generalized anaphylactic reaction/shock. Severe *physiologic* reactions include treatment-resistant vasovagal reactions, arrhythmia, hypertensive emergencies, and convulsions/seizures. Also, to this category belong pulmonary oedema and cardiopulmonary arrest (ACR, 2022; ESUR, 2018; Wang, 2008).

Risk factors

Risk factor analysis is often done by retrospective observational studies without control groups (see also chapter 3.5.3 Risk Factors for Hypersensitivity Reactions to Contrast Media). Risk factors for hypersensitivity are not fully established. Additional risk factors for immediate HSR that are common to allergic drug reactions include poorly controlled bronchial asthma, concomitant medications (e.g., ACE inhibitors, ß- blockers, and proton pump inhibitors), rapid administration of the drug, mastocytosis, autoimmune diseases, and viral infections (Rosado Ingelmo, 2016).

In Radiology literature, the most consistently reported risk factors for hypersensitivity reactions to CM are (ACR, 2022):

1. A prior hypersensitivity reaction to contrast media.
2. A history of allergy, particularly multiple severe allergies (atopy).
3. A history of asthma requiring treatment.

Female gender could not be substantiated as an independent risk factor for hypersensitivity reactions, but age may be relevant (Endrikat, 2022).

**Incidence of acute hypersensitivity reactions**

Incidence after iodine-based contrast media
The incidence is highest after iodine-based contrast media and lowest after ultrasound contrast agents. The incidence of acute adverse reactions has declined considerably after the introduction of low-osmolar and iso-osmolar iodine-based contrast media (ACR, 2022; ESUR, 2018).

In the early days of low-osmolar media, the classic Japanese study (Katayama, 1990) reported relatively high adverse drug reaction rates after nonionic CM of up to 3,1%, with severe and very severe reactions occurring in 0,44%. In contrast, more recent studies with large patient cohorts focusing more specifically on hypersensitivity (allergic-like) reactions have shown considerably lower incidence rates of 0,15 to 0,69% with severe reactions occurring in 0,005 to 0,013% (Hunt, 2009; Mortele, 2005; Wang, 2008).

Hypersensitivity reactions after non-vascular CM administration (either oral, rectal, intraductal, intravesical or intra-articular) are rare (see also the overview in Safe Use of Contrast Media, part 2). Such reactions occur slower, and the incidence is much lower than after intravascular administration and will be influenced by the integrity and condition of the wall of the cavity into which the contrast agent is administered (for example inflamed mucosa may lead to leakage into the intravascular compartment). Nevertheless, severe reactions can occur, even with non-vascular CM administration (Davis, 2015).

Incidence using specific iodinated contrast media
Large post-marketing surveillance studies of iobitridol and iodixanol have shown acute adverse events of 0,58-0,59% with severe events in 0,004 to 0,010% (Maurer, 2011; Zhang, 2014). A third study using iopromide is more difficult to compare due to different definitions, and had higher rates of 2,49% and 0,034%, respectively (Palkowitsch, 2014). It must be noted that physiologic reactions (feeling of warmth, metallic taste) make up a considerable part of these events.
More recently, the hypersensitivity reaction rate after iopromide was 0,74% in adults and 0,38% in elderly (Endrikat, 2022). In the same study population, the hypersensitivity reaction rate was 0.7% after intravenous administration vs. 0.2% after intra-arterial administration (Endrikat, 2020).

In addition, several retrospective observational studies have looked at differences in acute hypersensitivity rates among iodine-based CM. Although imperfect, these studies indicate a somewhat higher rate for iopromide and iomeprol compared to other CM (An, 2019; Gomi, 2010; Kim, 2017; Seong, 2014). It remains controversial whether iobitridol has a lower percentage, as indicated in one study (Kim, 2017).

Incidence after gadolinium-based contrast agents
Recent studies in large adult patient cohorts focusing on hypersensitivity (allergic-like) reactions have shown low incidence rates of 0,06-0,17% with severe reactions occurring in 0,003-0,006% (Aran, 2015; Behzadi, 2018; Dillman, 2007; Prince, 2011). More recent studies showed overall rates of 0,15-0,40%. For severe reactions rates were 0,002-0,004% in general populations and 0,033% in a population undergoing cardiac MRI (Ahn, 2022; McDonald, 2019; Uhlig, 2019).

In a large meta-analysis, the overall rate was 92 per 100,000 gadolinium-based contrast agent (GBCA) injections (0,09%) with severe reactions occurring in 5,2 per 100,000 injections

(0,005%). It was shown that the type of GBCA is of influence on the number of reactions. Linear nonionic GBCA had an incidence of 15 per 100,000 and linear ionic GBCA of 52 per 100,000. However, these GBCA are no longer available in Europe. The macrocyclic GBCA had slightly higher rates, macrocyclic ionic GBCA 90 per 100,000 and macrocyclic nonionic GBCA 160 per 100,000. The highest rate was for linear ionic GBCA with protein-binding, 170 per 100,000 injections (Behzadi, 2018).

Comparing specific GBCA, in one study more hypersensitivity reactions occurred after gadobenate and gadobutrol compared with gadodiamide or gadoterate injection (McDonald, 2019), while in another study most acute reactions occurred with gadoteridol and most delayed reactions with gadoterate (Ahn, 2022).

**Breakthrough, protracted and biphasic hypersensitivity reactions**

So-called “breakthrough” hypersensitivity reactions are recurring reactions despite premedication with corticosteroids and H1-antihistamines. The occurrence in published series is variable, 2 to 17%. These reactions are most often of similar severity as the original (culprit) reaction for which premedication was prescribed. Breakthrough reactions can be severe in incidental cases. Unfortunately, no data on the number of IgE-mediated reactions are available (Davenport, 2009; Mervak, 2015).

While most hypersensitivity reactions to CM are uniphasic, other patterns may also occur. A *protracted* reaction is defined as a reaction lasting > 5h in which symptoms incompletely resolve. This pattern is rare following CM, occurring in only 4% of anaphylactic (severe) reactions and may be predicted by a low responsiveness to initial adrenaline therapy (Kim, 2018).

A *biphasic* reaction is defined as a reaction recurring 0 to 72h after an initial hypersensitivity reaction. The median time for start of the second reaction is 8 to 12h after the first reaction. This pattern is also rare, occurring in 10% of anaphylactic (severe) reactions (Rohacek, 2014). Usually, the second reaction is of similar severity or milder than the initial reaction.
Predictors for biphasic anaphylaxis are severe initial symptoms requiring adrenaline redosing or a long (> 40 min) duration of the initial reaction. An observation time of 6-12h after the initial anaphylactic reaction has resolved is practical (Lee, 2016; Kim, 2018 and 2019). The use of corticosteroids in this setting is controversial and is not recommended (Gabrielli 2019; Lee, 2016; Simons, 2015).

For ultrasound contrast agents the risk is low, but no large series have been published to date. Most adverse reactions are cardiovascular, and the incidence of hypersensitivity reactions is 0,009% with severe reactions occurring in 0,004% (Khawaja, 2010).

**Classification**
Historically, hypersensitivity reactions to CM have been graded as mild, moderate, or severe. This radiological classification shows overlap with other used classifications, such as the World Allergy Organisation (WAO) classification (Johansson, 2004) and modifications of the Ring - Messmer classification of allergic reactions (Ring, 1977; Table 1).

**Table 1** ***Severity grading of anaphylactic reactions*** **(modified Ring and Messmer)**

| Grade | Skin | Abdomen | Airways | Cardiovascular |
|---|---|---|---|---|
| I | Itch Flush Urticaria Angioedema | - | - | - |
| II | Itch Flush Urticaria Angioedema | Nausea Cramps | Rhinorrhoea Hoarseness Dyspnoea | Tachycardia (> 20 bpm) Hypertension (>20 mm Hg) Arrhythmia |
| III | Itch Flush Urticaria Angioedema | Vomiting Defecation | Laryngeal oedema Bronchospasm Cyanosis | Shock |
| IV | Itch Flush Urticaria Angioedema | Vomiting Defecation | Respiratory arrest | Cardiac arrest |
| *Classification according to the most severe symptom, no symptom is mandatory* | | | | |

A practical summary classification of acute hypersensitivity reactions to contrast media for radiological practices may be (free after ACR, 2022; ESUR, 2018):

**Mild:** Itching, sneezing, flushing, conjunctivitis, rhinorrhoea, epiphora, nausea, short- duration, or incidental vomiting, altered taste, limited (localized) scattered urticaria.
**Moderate:** Generalized or extensive urticaria, diffuse erythema without hypotension, facial or angioedema without dyspnoea, mild wheezing/bronchospasm, protracted vomiting, mild isolated hypotension.
**Severe:** Severe wheezing/bronchospasm, profound hypotension, pulmonary oedema, generalized anaphylactic reaction, seizures/convulsions, respiratory arrest, and cardiac arrest.

It is important to note that re-exposure to CM after an initial mild reaction never causes a moderate or severe reaction (Lee, 2017; Davenport, 2009). In addition to this, the risk of an IgE-mediated allergic reaction (and thus the risk of severe reactions in case of re-exposure) is low in moderate reactions without cutaneous symptoms. Therefore, in the classification most used in allergology only reactions with cutaneous symptoms (urticaria or angioedema) are classified as allergic-like (Torres, 2021).

**Nonimmediate (late, delayed) hypersensitivity reactions to Contrast Media**

**Clinical features**
A nonimmediate hypersensitivity reaction (NIHR) is a delayed hypersensitivity reaction > 1h after contrast administration (usually > 24h). NIHR usually presents as a maculopapular exanthema (MPE): skin rash consisting of patches (maculae) and nodules (papulae) spread over body and extremities. It normally heals within days to weeks, and if treatment is required, topical or oral steroids can be applied.

Many patients show a variety of nonspecific symptoms, which include headache, nausea, dizziness, gastro-intestinal upset, mild fever, and arm pain (Bellin, 2011; Christiansen, 2000). When compared to control populations (Loh, 2010), skin rashes with erythema and swelling are the most frequent true nonimmediate hypersensitivity reactions. Most patients present with cutaneous symptoms like other drug-induced skin eruptions, usually in the form of a macular or maculopapular exanthema. The exanthema usually occurs 2 to 10 days after first exposure to ICM and 1 to 2 days after re-exposure to the same ICM. Most reactions are mild to moderate in severity, are usually self-limiting and resolve within 1 week (Bellin, 2011).

Discrimination should be made between mild-to-moderate NIHR and rare severe NIHR with danger signs, the so-called severe cutaneous adverse drug reactions (SCAR), such as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, toxic epidermal necrolysis (TEN), acute generalized exanthemic pustulosis (AGEP), and Stevens-Johnson syndrome (SJS) (Brockow, 2019; Soria, 2021).

**Pathophysiology**
There is evidence that drug-specific T-cells play an important role in nonimmediate hypersensitivity reactions. In skin reactions an infiltrate in the dermis consisting of activated $CD4^+$ or $CD8^+$ T-cells and eosinophils is usually found (Christiansen, 2000 and 2003; Schönmann, 2020).

*In vitro* studies have shown two different pathways of CM recognition which both require major histocompatibility complex (MHC) molecules for stimulation: a) direct binding of CM to the T-cell receptor or MHC molecule (p-i concept), and b) after uptake and processing by antigen-presenting cells and presented to T-cells via MHC-II molecules ((pro)hapten concept) (Keller, 2009).

The hapten-independent pathway could explain results of cross-reactivity analyses that revealed that CM-specific activated T-cell clones reacted to CM with shared structural elements.

It has been postulated that CM do not induce a primary immune response, but instead interact with receptors on activated memory T-cells raised against other foreign substances (non-allergic NIHR). Patients with nonimmediate hypersensitivity should not be at risk for an immediate hypersensitivity reaction (mediated by IgE or other mechanisms) upon re- exposure to CM.

**Risk factors**
Established risk factors for nonimmediate hypersensitivity reactions to iodine-based CM include a previous hypersensitivity reaction and IL-2 immunotherapy. Most CM-associated nonallergic NIHR are associated with iso-osmolar CM (ACR, 2022; Bellin, 2011; ESUR, 2018).

Patients with a history of nonimmediate hypersensitivity reactions to ICM are not at increased risk for immediate HSR to ICM as these reactions are mechanistically unrelated (Christiansen, 2003; Mazori, 2018).

**Incidence of nonimmediate hypersensitivity reactions**
The frequency of nonimmediate hypersensitivity reactions to CM varies greatly between studies and is believed to be between 1-3% of patients after iodine-based CM administration and only very rarely after gadolinium-based CA administration (Bellin, 2011; Christiansen, 2000).

Incidence using specific iodine-based CM
Nonimmediate skin reactions tend to be more common after iodixanol (Benin, 2011; Sutton, 2003). The incidence of nonimmediate hypersensitivity reactions is not significantly different for the other iodine-based low-osmolar CM (Bellin, 2011).

**Cross-reactivity between contrast media**

*Cross-reactivity between iodine-based CM*
Most of the current cross-reactivity data come from skin testing. Cross-reactivity in late hypersensitivity reactions is probably caused by the presence of CM-specific T-cells, some of which may show a broad cross-reactivity pattern. There may be a link between the chemical structure of iodine-based CM and the pattern of cross-reactivity, but results are inconsistent.

Several studies have shown considerable cross-reactivity between different iodine-based CM, but specific data on immediate versus nonimmediate hypersensitivity reactions are lacking until now. In the larger studies, most cross-reactivity has been seen between the nonionic dimer iodixanol and its monomer iohexol, with relatively fewer positive skin reactions with iobitridol (Clement, 2018; Hasdenteufel, 2011; Lerondeau, 2016; Yoon, 2015).

Based on cross-reactivity patterns iodine-based CM may be divided in three groups, with relatively high intra-group cross-reactivity but less intergroup cross-reactivity (Lerondeau, 2016). Based on additional data, it seems reasonable to add iopromide to group A as well and possibly remove ioxithalamate and iopamidol (Schrijvers, 2018).

Table 2 may be helpful for selecting an alternative agent for imaging studies.

**Table 2 Cross-reactivity grouping of iodine-based CM (Lerondeau, 2016)**

| Group A | Group B | Group C |
|---|---|---|
| Ioxithalamate (Telebrix) | Iobitridol (Xenetix) | Amidotrizoate (Gastrografin) |
| *Iopamidol (Iopamiro)* | *Ioxaglate (Hexabrix)* | |
| Iodixanol (Visipaque) | | |
| Iohexol (Omnipaque) | | |
| Ioversol (Optiray) | | |
| Iomeprol (Iomeron) | | |
| Iopromide (Ultravist) | | |

*Note: Iopamidol and Ioxaglate are no longer available on the market in The Netherlands*

Cross-reactivity between gadolinium-based CM
Information on cross-reactivity between GBCA is limited to case reports. Skin testing and provocation tests in such cases have shown that cross-reactivity among macrocyclic GBCA may be more extensive than among linear GBCA (Gallardo Higueras, 2021; Grüber, 2021).

Cross-reactivity between iodine-based and gadolinium-based CM
A recent study examined the risk of reactions to both iodine-based CM and gadolinium- based CA in the same patient in a large patient cohort. The incidence of primary hypersensitivity reactions was 0,047% and the incidence of secondary reactions 0,024%. Nearly all reactions were mild, requiring no treatment. Therefore, cross-reactivity between iodine-based and gadolinium-based CM is an extremely rare event (Sodagari, 2018).

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

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# In vitro testen bij patiënten met hypersensitiviteitsreacties na CM

## Uitgangsvraag

Wat is de diagnostische waarde van serum en/of urinetesten voor contrastmiddel-geïnduceerde hypersensitiviteitsreacties?

## Aanbeveling

Meet serum tryptase, het liefst binnen 1-2 uur (tussen 15 minuten en 4 uur) vanaf de start van alle matige tot ernstige acute hypersensitiviteitsreacties na contrastmiddeltoediening. Deze meting dient als baseline voor verder allergologisch onderzoek.
*Zie ook flow charts

Basofiele activatietesten zijn gereserveerd voor selecte patiënten met matige tot ernstige acute hypersensitiviteitsreacties, en zijn alleen beschikbaar in gespecialiseerde allergologiecentra.

Voor niet-acute hypersensitiviteitsreacties zijn geen noemenswaardige in-vitro testen beschikbaar in Nederland.

## Overwegingen

1. Immediate/acute hypersensitivity reactions (IHR)

*Tryptase*
Histamine and tryptase can be both measured to confirm IHR to CM. However, histamine is degraded quickly, being less specific and more complicated to measure by commercially available assays. Thus, tryptase is regarded as the preferred mediator. The approach is to compare acute (within 4 hours of the event) and baseline total tryptase levels (at least 24 hours after all signs and symptoms of the event have subsided) to distinguish between an increased mast cell burden (e.g., mastocytosis, in which baseline tryptase levels remain elevated) and mast cell degranulation (with only acute tryptase levels elevated). The minimal elevation of acute over baseline tryptase levels suggested to be clinically significant is calculated as at least 2 ng/mL + [1.2 x baseline tryptase level] (Sprung, 2015) or at least 20% above baseline plus 2 ng/mL during or within 4 hours after a symptomatic period (Valent, 2012). An increase from baseline level during allergic symptoms is suggestive of an IHR to CM. It has been reported that higher tryptase elevations are indicative of IgE-mediated mast cell activation and correlate with the clinical severity of the reaction (Clement, 2018; Laroche, 2005; Schwarz, 2006).

Therefore, the ESUR guidelines suggests serum tryptase measurements following a suspected immediate hypersensitivity reaction. The minimum recommendation is one sample 1 to 2 hours after the reaction point. Ideally, three samples should be obtained, the first one once this histamine release is underway, the second at 1 to 2 hours after the reaction, and the third at 24 hours or during convalescence (ESUR, 2018). The recently published practice guideline by the European Academy of Allergy and Clinical Immunology (EAACI) considers tryptase determination in the acute phase useful for confirming IHR to CM, if a transient increase is detectable (strong/moderate) (Torres, 2021). It is advised to measure tryptase within 4 hours of the acute event.

*Basophil Activation Test (BAT)*
The BAT technique is based on detection of activation of basophils with flow cytometry. CD63 expression serves as a unique marker for identifying activated cells. The technique requires a small amount of fresh blood, less than 0.1 mL. The CD63 marker is located to the same secretory granule that contains histamine; in principle, histamine production could also be used as a marker of basophil activation, but determination of histamine is more cumbersome than detecting CD63 upregulation (Hoffmann, 2015).
BAT has shown its usefulness in diagnosing immediate hypersensitivity reactions to contrast media. The use of BAT in acute reactions to GBCA demonstrated an excellent specificity (93%) in the diagnosis of allergic immediate hypersensitivity to GBCA and a quite good sensitivity (69%). It was concluded that BAT remains especially useful for patients with uncertain diagnosis and to confirm a positive ST result (Kolenda, 2018).
Three studies published on the diagnostic value of BAT regarding CM. The sensitivity ranged from 46 to 63%, while specificity varied between 89 and 100% (Pinnobphun, 2011; Salas, 2013; Trcka, 2008). Pinnobphun et al. also reported an area under the ROC curve of 0.79 by using the stimulation index as the diagnostic criteria with 1:100 dilution of radiocontrast media (Pinnobphun, 2011).

Thus, BAT can be a complementary tool to diagnose IHR to CM (Brockow, 2020), showing good correlation with ST and DPT results (Salas, 2013). Since it is an *in vitro* test, it may be especially useful in cases with severe reaction and contraindications for ST or DPT (Brockow, 2020). However, there are several limitations to consider. The NPV has not been clearly determined (Decuyper, 2017) and that certain factors may affect BAT result, such as the time between the reaction and the test or the severity and type of reaction (Salas, 2013). In addition, it has to be considered that more than 10% of patients have non-reacting basophils

(i.e., the positive control remains negative), rendering this test unsuitable for these patients at that time. Lastly, BAT is currently only available in specialized drug allergy centres in the Netherlands. The EAACI practical guidelines (Torres, 2021) consider BAT an additional tool for diagnosing patients with IHR with severe reactions or those with high risk (weak/low).

2. Nonimmediate/late hypersensitivity reactions (NIHR)

*Lymphocyte Transformation Test (LTT)*
LTT is not recommended at the acute stage, but after 4-8 weeks after remission (Hari, 2011) and within 2 -3 years after the reaction (Pichler, 2004). Corticosteroids in doses higher than
0.2 mg/kg prednisone equivalent and other immunosuppressive or immunomodulatory agents may interfere with the test. A NPV for LTT in NIHR to CM is not available. As radioactive materials have been banned in many laboratories, the use of "modified non- radioactive LTT" will be a better choice.
The LTT is recommended as an additional diagnostic tool in selected cases with contraindications for STs (weak/low). It should only be performed by experienced physicians (weak/low) (Torres, 2021). Unfortunately, LTT is currently not available in any allergology centre in the Netherlands. Alternative *in vitro* tests such as the OX40 test are still under development.

Measure serum tryptase, preferably between 1-2 hours (range 15 minutes to 4 hours) from the start of all moderate to severe immediate hypersensitivity reactions to contrast media. This measurement serves as a baseline for further allergologic examinations.

*See also flow charts

Basophil activation tests are reserved for selected patients with moderate to severe acute hypersensitivity reactions and are only available in specialized drug allergy centres.

For nonimmediate hypersensitivity reactions there are no meaningful *in vitro* tests available in the Netherlands.

## Onderbouwing

### Achtergrond

*In vitro* tests using blood or urine can be employed in the analysis of possible hypersensitivity reactions, immediately following the event or in an outpatient setting. Which diagnostics should be performed depends on the timing and the type of reaction.

Hypersensitivity reactions to contrast media are described as immediate (acute) or nonimmediate (delayed, late). Reactions occurring within one hour after application of the agents are coined as immediate, reactions occurring later are called nonimmediate. For more information see the Introduction of this chapter.

Nonimmediate hypersensitivity reactions (NIHM) are mediated by CM specific T- lymphocytes (Christiansen, 2000; Kanny, 2005; Lerch, 2007; Romano, 2002). In the (semi)acute setting, there are no *in vitro* diagnostic methods available to confirm the diagnosis. To date, only a skin biopsy can be useful in this setting, but specific pathognomonic features are lacking. Routine laboratory diagnosis (leukocyte count + differential, liver enzymes, urea, creatinine) is useful to screen for extracutaneous organ involvement. Eosinophilia may support the diagnosis of NIHM but lacks both sensitivity and specificity.
Additional diagnostic methods in the outpatient setting are also mostly performed *in vivo* by means of patch testing and/or skin prick or intradermal testing with late (>24 hours) readings. Lymphocyte transformation tests (LTT) are currently not available in the Netherlands.

Immediate hypersensitivity reactions (IHR) are nowadays considered to be mediated by both allergic (IgE-mediated) and nonallergic (non-IgE-mediated, i.e., direct nonspecific mast cell degranulation or complement activation) mechanisms (Torres, 2021).

In the acute event of an IHR, mast cell degranulation (via IgE or non-IgE mediated mechanisms) can be studied by measuring serum beta-tryptase (tryptase) or histamine. Serum histamine determination is unpractical because of its short half-life in circulation. An alternative is detection of histamine metabolites in

urine. (N-τ-Methylhistamine). Although this is a reliable parameter (Keyzer, 1984), very few laboratories have this test in their routine repertoire, and there are not enough data available with respect to contrast media. So, this parameter is not further discussed.

In the outpatient setting, analysis of IHR mostly depends on *in vivo* diagnostic methods using skin prick and intradermal testing. In the recent years, additional drug provocation tests (DPT) have gradually been implemented in specialized centres. *In vitro* diagnosis is limited to detection of specific IgE antibodies and basophil activation tests (BAT). Specific antibodies against certain ionic contrast media have been detected in patients with IHR (Laroche 1998;

Mita 1998); however, to date there are no specific IgE antibodies commercially available. Application of BAT to heparin stabilized blood samples of patients shows interesting results but its availability is limited to specialized laboratories.

### Samenvatting literatuur

No studies were included in the analysis of the literature; therefore, no systematic literature analysis was performed.

### Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: What is the diagnostic value of serum and/or blood testing compared to clinical diagnosis of hypersensitivity reaction after contrast administration / no *in vitro* tests for contrast media induced hypersensitivity reactions?

**P** (Patients) Patients with hypersensitivity reactions after undergoing radiological examinations with contrast media.
**I** (Intervention) Serum tests: tryptase, blood test, basophil activation test.
**C** (Comparison) Clinical diagnosis of hypersensitivity reaction after contrast administration / no serum tests.
**R** (Reference test) Drug provocation test.
**O** (Outcomes) Correctly confirmed diagnosis of hypersensitivity reaction to contrast media (sensitivity, specificity, area under the curve, positive predictive value PPV, negative predictive value NPV).

Relevant outcome measures
The working group considered sensitivity and specificity critical outcome measures for the decision-making process; and considered the area under the curve and the positive and negative predictive values important outcome measures.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until April 22nd, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 368 hits. Studies were selected based on the following criteria:

- Adult patients with hypersensitivity reaction to radio contrast media.
- Evaluation of diagnostic properties of serum tests to contrast media.

- Application of a provocation test to confirm results of cutaneous testing.
- Reports predefined outcome measures: sensitivity, specificity, area under the curve, positive predictive value, negative predictive value.
- Serum tests tryptase and urine-metabolites should be performed within 24 hours after hypersensitivity reaction.
- No reports of case series or exploratory findings (n≥10).

Seven studies were initially selected based on title and abstract screening. After reading the full text, all seven studies were excluded (see Table of excluded studies in 'Appendices to modules').

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

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# Diagnostische waarde van huidtesten voor hypersensitiviteitsreacties na CM

## Uitgangsvraag

Wat zou gedaan moeten worden bij patiënten met een geschiedenis van hypersensitiviteitsreacties na contrastmiddel (CM)-toediening om het risico op herhaling van hypersensitiviteitsreacties te voorkomen?

## Aanbeveling

Verwijs de patiënt naar een allergoloog om huidtesten uit te voeren met het te verwachten oorzakelijke CM en met diverse alternatieve CM, bij voorkeur binnen 6 maanden na de hypersensitiviteitsreactie.

Doe dit bij de volgende patiëntengroepen:

- Matige tot ernstige acute hypersensitiviteitsreacties door een CM
- Ernstige mucocutane niet-acute hypersensitiviteitsreacties door een CM
- Hypersensitiviteitsreacties op twee of meer verschillende CM van hetzelfde type (bijvoorbeeld twee verschillende jodiumhoudende CM) of twee of meer types CM (bijvoorbeeld een jodiumhoudend CM en een gadoliniumhoudend CM)
- Alle patiënten met een doorbraak hypersensitiviteitsreactie ondanks premedicatie met corticosteroïden en/of H1-antihistaminen

Specificeer altijd het gebruikte CM in de verwijzing naar de allergoloog.

Zie ook flow charts

## Overwegingen

In a meta-analysis of skin testing the pooled per patient positivity rate increased with the severity of the hypersensitivity reaction, and skin testing was especially useful in more severe reactions (Yoon, 2015).

The status of skin testing in immediate HSR to ICM has recently been summarized excellently by the European Association of Allergy and Clinical Immunology (EAACI) in their Practice Parameters 2021 (Torres, 2021), and the committee decided to adhere and follow these recommendations that are outlined below. The same can be followed for immediate HSR to GBCA.

Testing will adhere to the general European Network of Drug Allergy – European Association of Allergy and Clinical Immunology standards (Brockow, 2002; Brockow, 2013; Torres, 2021). Intradermal testing has high sensitivity to identify allergic hypersensitivity reactions (Trautmann, 2019).

Non-severe nonimmediate HSR is often an MPE, which is self-limiting and resolves within 7 days (Bellin, 2011). In case of nonimmediate HSR the negative predictive value of skin testing is considerably lower than in immediate HSR (Caimmi, 2010; Kim, 2013; Meucci 2020; Salas, 2013; Sesé, 2016; Torres, 2012*)*.
Because of the mild symptomatic burden of these patients and the limitatons of allergologic skin testing the committee decided to not adhere to the EAACI guideline (Torres, 2021) and recommend against referral for skin testing in these patients.

It is the GDG opinion that change of CM is a more effective approach in patients with non- severe non-immediate HSR. Thereby it is important to note that nonionic dimeric ICM induce significantly more often cutaneous NIHRs than nonionic monomeric ICM. In fact, more than 50% of MPE are induced by the iso-osmolar ICM (Torres, 2021)

A. *Immediate Hypersensitivity Reactions*

Recommendations how to perform skin testing:

- When to test: STs are preferably performed within 2-6 months after the reaction. Performing STs < 1 month or > 12 months is expected to lower sensitivity.
- What to test: STs should be performed with the ICM involved in the reaction if known. If the result is positive or if the culprit ICM is unknown, STs should be performed with the broadest possible panel of ICM.
- How to test: ICM should be used undiluted at 300- 320 mg/mL for SPT and diluted at 1:10 for IDT. Addition of undiluted IDT may increase sensitivity but should be interpreted with caution. STs should start by performing SPT and, if negative, continue with IDT.

B. *Nonimmediate hypersensitivity reactions*

Recommendations how to perform skin testing:

- When to test: for non-SCAR reactions, more than 4 weeks after the skin lesions have resolved but ideally within the first 6 months after the clinical reaction. Wait > 6 months in case of DRESS or AGEP
- What to test: ideally the suspected culprit and several commonly used alternatives due to the extended cross-reactivity in nonimmediate HSR. In DRESS and FDE, patch tests can be useful and SPT and IDT should preferably not be used directly, or in lower concentrations.
- How to test: IDT with 1:10 dilution of the standard concentration of ICM or undiluted on the upper arm or upper back with delayed reading after 48 and 72 hours. PT on the upper back with undiluted standard solution of ICM with reading at 48 hours and a delayed reading (72-120 hours). Patients should be instructed to return for additional readings in case of any later appearing skin reaction at the test site. Using both tests may enhance sensitivity.

If all tests are negative: Consider IDT and/or PT with undiluted CM in local testing, especially in FDE.

**Table 1 Positive rates of cutaneous tests in patients with immediate HSR to ICM**

| | | Positive rate of skin tests, % | | Positive rate of IDT, % Severity of HSR | | |
|---|---|---|---|---|---|---|
| | | SPTa | IDTb | Mild | Moderate | Severe |
| Brockow, 2009 | ICMc | 3 (4/122) | 26 (32/121) | 26 (24/92) | - | 28 (8/29) |
| Caimmi, 2010 | ICMc | 0 (0/101) | 15 (15/101) | - | - | - |
| Dewachter, 2001 | ICMc | 50 (2/4) | 100 (4/4) | - | - | 100 (4/4) |
| Dewachter, 2011 | ICMc | 4 (1/24) | 46 (12/26) | 33 (3/9) | 40 (4/10) | 71 (5/7) |
| Goksel, 2011 | ICMc | 0 (0/14) | 14 (2/14) | 14 (1/7) | 14 (1/7) | - |
| Kim, 2013 | ICMc | 3 (1/32) | 26 (12/46) | 13 (4/31) | 25 (2/8) | 57 (4/7) |
| Kim, 2014 | ICMc | 2 (1/51) | 65 (33/51) | - | 18 (2/11) | 78 (31/40) |
| Meucci, 2020 | ICMc | 0 (0/) | 10 (10/98) | | | 23 (3/13) |
| Pinnobphun, 2011 | ICMc | 0 (0/63) | 24 (15/63) | 23 (12/53) | 0 (0/5) | 60 (3/5) |
| Prieto-Garcia, 2013 | ICMc | 0 (0/106) | 10 (11/106) | 9 (6/66) | 14 (4/29) | 9 (1/11) |
| Renaudin, 2013 | ICMc | 14 (1/7) | 57 (4/7) | - | - | 57 (4/7) |
| Salas, 2013 | ICMc | 3 (3/90) | 6 (5/90) | 0 (0/69) | 11 (2/18) | 100 (3/3) |
| Schrijvers, 2019 | ICMc | 13 (80/597) | | Anaphylaxis grade 3-4 had a 6.8-fold (95%CI 3.2-14.5) increased risk for skin test positivity | | |
| Sesé, 2016 | ICMc | 3 (1/37) | 13.5% (5/37) | 11 (4/37) | 3 (1/37) | - |
| Trcka, 2008 | ICMc | - | 4 (4/96) | 0 (0/40) | 7 (3/44) | 8 (1/12) |

aSPT = Skin Prick Test; bIDT= Intradermal Test; clodine-based Contrast Media

**Performing and Reporting Skin Testing for Contrast Media**

Most hospitals nowadays have contracts with just a few contrast media vendors. For skin testing of contrast media, however, it is important to test a panel of contrast agents (ICM and/or GBCA), including the culprit contrast agent and potential alternatives. Such a panel could be individualized for the specific hospital (group) where the patient comes from.

To facilitate establishment of such a local panel of iodine-based and gadolinium-based agents for allergic skin testing, we have listed the available agents in The Netherlands and their indications below.

See for physicochemical characteristics of ICM and GBCA also Supplemental Tables S1 and S2.

**Table 2 Contrast agents in The Netherlands registered with the Medicine Evaluation Board**

| **Iodine-based contrast media** | | | |
|---|---|---|---|
| *Name* | *Commercial Name* | *Company* | *Main Indication* |
| Iopromide | Ultravist | Bayer Healthcare | Intravascular CT/Angio |
| Iomeprol | Iomeron | Bracco Imaging | Intravascular CT/Angio |
| Iohexol | Omnipaque | GE Healthcare | Intravascular CT/Angio |
| Iodixanol | Visipaque | GE Healthcare | Intravascular CT/Angio |
| Ioversol | Optiray | Guerbet | Intravascular CT/Angio |
| Iobitridol | Xenetix | Guerbet | Intravascular CT/Angio |
| | | | |
| Amidotrizoate meglumine | Gastrografine | Bayer Healthcare | Gastrointestinal RF/CT |
| Ioxithalamate meglumine | Telebrix Gastro | Guerbet | Gastrointestinal RF/CT |
| | | | |
| **Gadolinium-based contrast agents** | | | |
| *Name* | *Commercial Name* | *Company* | *Allowed Indication* |
| Gadobutrol | Gadovist | Bayer Healthcare | Total Body MRI |
| Gadoteridol | ProHance | Bracco Imaging | Total Body MRI |
| Gadoterate meglumine | Dotarem/Artirem | Guerbet | Total Body MRI |
| | Clariscan | GE Healthcare | Total Body MRI |
| | Dotagraf | Bayer Healthcare | Total Body MRI |
| Gadoxetate disodium | Primovist | Bayer Healthcare | Liver MRI |
| Gadobenate dimeglumine | MultiHance | Bracco Imaging | Liver MRI |
| Gadopentetate meglumine | Magnevist | Bayer Healthcare | MR Arthrography |
| | | | |

*See also: https://www.geneesmiddeleninformatiebank.nl/nl/*

Documentation

When reporting skin tests, it is optimal that the allergologist gives a clear written recommendation in the electronic patient dossier about:

1. The possible ICM and/or GBCA that can be used in future CM-enhanced studies
2. The use of or need for specific prophylactic measures in future CM-enhanced studies if applicable

**Recommendations**

Refer the patient to a drug allergy specialist to perform skin tests for the suspected culprit and several commonly used alternatives, ideally within 6 months after the hypersensitivity reaction.

Refer the following patient groups:

- Moderate to severe immediate hypersensitivity reactions to a contrast medium
- Severe mucocutaneous non-immediate hypersensitivity reactions to a contrast medium
- Hypersensitivity reactions to two or more different contrast media (e.g., two different iodine-based contrast media or gadolinium agents, or an iodine-based contrast medium and a gadolinium-based contrast agent)
- All patients with breakthrough hypersensitivity reactions despite premedication with corticosteroids and/or H1-antihistamines

Always specify the used contrast medium in the referral to the drug allergy specialist.

## Onderbouwing

### Achtergrond

Hypersensitivity reactions to contrast media (CM) have traditionally been classified as non- allergic reactions, and skin tests have been regarded as inappropriate tools in patients having experienced such reactions. However, during the last years several investigators have reported positive skin tests in patients with both immediate and nonimmediate hypersensitivity reactions after CM exposure, which indicates that immunological mechanisms may be involved more frequently than previously thought (Brockow, 2009 and 2020). In this chapter the diagnostic value of cutaneous tests for CM hypersensitivity reactions is assessed, which may serve as a more valid alternative to prophylactic medication for CM reactions. Furthermore, the working group evaluates whether these skin tests should be recommended in clinical practice, and under which conditions.

### Conclusies / Summary of Findings

| | |
|---|---|
| **Very Low GRADE** | The negative predictive value of the cutaneous test is estimated to be 80 to 97% for immediate hypersensitivity reactions to contrast media.<br><br>The negative predictive value of the cutaneous test is estimated to be 58-86% for nonimmediate hypersensitivity reactions to contrast media.<br><br>*Caimmi, 2010; Kim, 2013; Meucci 2020; Salas, 2013; Sesé, 2016; Torres, 2012* |

### Samenvatting literatuur

Description of studies

1. *Diagnostic characteristics of cutaneous tests for **immediate** HSR*

The diagnostic characteristics of cutaneous tests for acute (immediate) hypersensitivity reactions (HSR) to contrast media (CM) were evaluated in 4 studies (Caimmi, 2010; Kim, 2013; Salas, 2013; Sesé, 2016).

Caimmi (2010) studied 159 patients. Patients were tested with the culprit iodine-based contrast medium (ICM) and a set of other ICM if they were positive for the culprit ICM or if its name was unknown. To know which ICM was involved, either patients already knew which drug had supposedly caused the reaction, or the authors contacted the hospital in which the reaction had occurred. The ICM used were: amidotrizoate, ioxithalamate, iopamidol, iohexol, ioversol, iopromide, iomeprol, iobitridol, iodixanol and ioxaglate. Skin tests were performed firstly as prick tests with the undiluted commercially available solution and then, if negative, by intradermal tests (IDT) at a 1: 10 dilution. Prick tests were considered positive if, after 15 min, the size of the weal was at least 3 mm in diameter. For IDT, positivity was considered when the size of the initial weal increased by at least 3 mm in diameter after 15 to 20 min, considering as non-irritant a maximum dilution of 1/10. The negative predictive value was defined as the proportion of patients with negative skin test results to at least one ICM at first testing who had a further injection with that ICM without reacting. One hundred participated (75.5% participation rate). Seventy-one of them (59.2%) were females of a median age of 56 (45–65) years. Most of the reactions were immediate (101 out of 120, 84.2%), and in two cases, it was not possible to assess whether the reaction was immediate or nonimmediate. For immediate reactions, 42 (41.6%) were of grade 1, 34

(33.7%) of grade 2, 20 (19.8%) of grades 3 and five (4.9%) of grade 4. Only one (5.9%) of the 17 nonimmediate reactions was moderate, all the others were mild (16 to 94.1%).

Kim (2013) retrospectively included 1048 patients. The mean (SD) age was 55.1 (14.5) years; 501 (47.8%) were male. Intradermal test with the RCM that was to be used in the pending nonionic CM-enhanced CT was performed just before the CT examinations. The nonionic CM used was iopromide, iomeprol, iohexol, and iodixanol. Intradermal tests were conducted on the volar surface of the forearm with a negative control, saline. A 1:10 solution of contrast medium (0.03 to 0.05 mL), which has been accepted as a non-irritating concentration, was gently injected into the skin to produce a small superficial bleb of 2 to 4 mm. Skin test positivity was determined when the diameter of the wheal increased by at least 3 mm, and surrounding erythema was observed after 15 to 20 minutes. If a patient had a negative response to skin tests, CT was performed as scheduled (provocation). Of the 376 patients previously exposed to CM, 61 (16.2%) had a history of at least 1 mild CM-associated reaction: 56 (91.8%) had immediate and 5 (8.2%) nonimmediate reactions.

Salas (2013) included 90 patients with a history of immediate HSR after contrast media (CM). Immediate HSR was classified according to the Ring and Messmer scale. Skin tests (ST) were carried out using the following CM: iobitridol, iomeprol, iodixanol, iohexol, ioversol, iopromide and ioxaglate. Prick tests were performed using undiluted CM and IDT using 10- fold dilutions. In those with a negative ST, a single-blind placebo-controlled provocation test was performed with the CM involved, as described. In patients with a positive ST and/or provocation test, a basophil activation test (BAT) was performed with iohexol (3; 0.3 mg/ml), iodixanol (3; 0.3 mg/ml), iomeprol (3.5; 0.35 mg/ml) and ioxaglate (5.8; 0.58 mg/ml) (based on dose–response curves

and cytotoxicity studies). The median age of the subjects evaluated was 54.50 ± 27 years; 63 (60%) were women. The CM involved in the reaction was iomeprol in 26 cases (28.89%), iodixanol in 19 (21.11%), iohexol in 11 (12.22%), iopromide in 9 (10.00%) and unknown in 25 (27.78%). According to the clinical history, most cases developed reactions with skin involvement (65.65% urticaria/ angioedema and 30% generalized erythema), and only 4.44% had airway or cardiovascular involvement. Regarding symptom severity, 69 cases (76.71%) had grade I reactions, 18 (20%) grade II and 3 (3.33%) grade III. No patients had grade IV reactions.

Sesé (2016) included 37 patients with a definite history of immediate HSR due to iodine- based contrast media (ICM). Immediate HSR was classified according to the Ring and Messmer scale. Skin tests were performed at least 6 weeks after the HSR on the volar forearm with the suspected ICM and with four other ICM. Skin prick tests (SPTs) involved freshly prepared undiluted ICM commercial solutions, and intradermal tests (IDTs) were performed successively with 100-fold and then 10-fold solution diluted in 0.9% sterile saline. Saline and chlorhydrate histamine were negative and positive controls, respectively. In total, 37 patients (24 women, mean age 49.3 years at the time of the reaction) completed the tests. The clinical severity of the reaction was grade I for 26 (70%), grade II for 4 (11%), and grade III for 7 (19%); 35 (95%) reported skin or mucosal symptoms, including pruritus (n = 11), facial erythema (n = 6), generalized erythema (n = 20), urticaria (n = 7), and angioedema (n = 5).

2. *Diagnostic characteristics of cutaneous tests for **non-immediate** HSR*

The diagnostic characteristics of cutaneous tests for delayed (nonimmediate) hypersensitivity reactions (HSR) to iodine-based contrast media (ICM) was evaluated in one study (Torres, 2012).

Torres (2012) included a total of 161 subjects with a history of a nonimmediate reaction imputable to at least one CM was evaluated. One patient who developed Stevens–Johnson syndrome was not included. The median age was 58.5 years (IR: 48.85 to 66.5) with 82 men (50.9%). According to the information obtained from the clinical history, the CM involved in the reaction were iomeprol in 53 (32.9%), iodixanol in 46 (28.6%), iohexol in 27 (16.8%),
iobitridol in 4 (2.5%), ioversol in 3 (1.9%), iopromide in 3 (1.9%), ioxaglate in 2 (1.2%) and
unknown in 23 (14.3%). According to the clinical history, 108 cases (67.1%) developed symptoms compatible with exanthema and 53 (32.9%) with delayed urticaria. Regarding symptom severity, 16 cases (9.9%) had mild reactions, 143 (88.8%) moderate reactions, and 2 severe reactions (1.2%) consisting of desquamative exanthema. Concerning the number of episodes, 132 cases (82%) had one episode and 29 cases (18%) two episodes.

3. *Other tests*

Three studies analysed different tests to determine hypersensitivity to contrast media (Kim, 2019; Meucci, 2020; Schrijvers, 2018).

Kim (2019) in a prospective cohort studied 36 patients with a history of immediate adverse drug reactions to radiocontrast media (RCM), presenting at the Allergy and Asthma Clinic of Severance hospital in South Korea

from 2017 to 2018. Mean age was 57.3 ± 13.9 years and 69.4% (n=25) was female. The index test was intradermal testing (IDT) with diluted (1:10) RCM: iobitridol, iohexol, iopamidol, iopromide, and iodixanol. The IDT was considered positive when the diameter of the initial wheal had increased ≥3mm and was surrounded by erythema, confirmed at 20 minutes and at 3 days after IDT. The comparator test was similar to the index test, only performed with undiluted RCMs. No reference test was performed.

Meucci (2020) studied retrospectively 98 patients with previous reactions to iodinated contrast media (ICM) presented at the Allergology Unit in a hospital in Italy, from 2015 to 2018. Median (range) age was 65.6 (23-90) years and 54.2% (n=53) was female. The index test was the (less sensitive) skin prick test with undiluted ICMs: iohexol, iopromide, iodixanol, iopamidol, and ioversol. The skin test was considered positive when the diameter of the initial wheal had increased ≥3mm and was surrounded by erythema after 15 minutes. Furthermore, a distinguishment was made between immediate hypersensitivity reactions (IHR) (<1 hour after ICM administration) and delayed hypersensitivity reactions (DHR) (>1 hour after ICM administration). The comparison test was an IDT with diluted (1:10) ICM: iohexol, iopromide, iodixanol, iopamidol, and ioversol. The IDT was considered positive
when the diameter of the initial wheal had increased ≥3mm and was surrounded by erythema after 20 minutes. The reference test was a DPT, where the choice of ICM was based on the following: in case of a mild, recent (<12 month) reaction with negative skin tests for the culprit ICM, the DPT was performed with the culprit ICM. In case participants refused administering of culprit ICM, or if culprit ICM was unknown, another ICM was chosen. A subgroup of patients was re-exposed to ICM as part of their regular medical care; this re-exposition was used as a reference test to analyse their entire diagnostic protocol (skin tests + DPT).

Schrijvers (2018) in a retrospective cohort studied 597 patients with a history of ICM- mediated drug hypersensitivity reaction, presenting at the Allergy Department of the University Hospital, France, February 2001 to September 2014. Median (range) age was 60 (13-92) years and 68.0% (n=406) was female. The index test was a skin prick test with undiluted ICM: amidotrizoate, ioxitalamate, iopamidol, iohexol, ioversol, iopromide,

iomeprol, iobitridol, iodixanol, and ioxaglate. The skin test was considered positive when the diameter of the initial wheal had increased ≥3mm and was surrounded by erythema after 15 minutes. When the skin test was negative, and intradermal test (IDT) was performed as well. The IDT was considered positive when the diameter of the initial wheal had increased ≥3mm and was surrounded by erythema after 20 minutes. No reference test was performed, but
re-exposure to a skin test negative ICM occurred in 233 (39%) patients as part of their regular medical care.

4. *Hypersensitivity reactions to gadolinium-based contrast agents (GBCA)*

For GBCAs there was even less literature available, as hypersensitivity reactions to these agents are infrequent with an estimated prevalence of 0.004%-0.7% (Ahn, 2022). Skin tests are performed only in case reports or small case series and outcome measures as NPVs can therefore not be calculated (Gallardo-Higueras 2021, Grüber 2021). As pathogenetic mechanisms for GBCA-mediated hypersensitivity reactions are considered similar to those elicited by ICM and skin tests are performed according to comparable protocols, the recommendations for GBCA are extrapolated from those for ICM.

Results

Due to the heterogeneity in study designs, reported outcomes and follow up times, pooling of data could not be performed.

1. *Diagnostic characteristics of cutaneous tests for **immediate** HSR*

Caimmi (2010) revealed that ICM skin tests were positive in 21 patients (17.5%). Seventeen of them (80.9%) had a history of immediate reaction (four with grade 1, eight grade 2, four grade 3 and one grade 4). Prick tests were all negative. IDT were positive at 20 min for 15 patients with an immediate history and for the patient with unknown chronology. Caimmi (2010) found one single false negative; the negative predictive value of ICM skin tests was 96.6% (95% CI: 89.9 to 103.2).

Kim (2013) showed that among the 1046 patients who had negative responses on skin tests, 52 (5.0%) showed immediate-type adverse reactions after CT using radio contrast media.
However, most reactions were mild and cutaneous, such as pruritus, urticaria, and mild angioedema. Only 1 patient (0.1%) had a grade II moderate immediate reaction accompanied by breathing difficulty and mild laryngeal oedema, which were relieved with an antihistamine. The negative predictive value of the pre-screening skin test for immediate hypersensitivity reactions before contrast media administration was 95.0%. The negative predictive value of the skin test for immediate hypersensitivity reactions in patients with a history of contrast media hypersensitivity reactions was 80.3% (n= 49/61) and that in patients without a history was 95.9% (n= 945/985).

Salas (2013) showed that five subjects (5.56%) had a positive skin test: three by prick test (one to iodixanol, one to iomeprol and one to iohexol) and five by intradermal testing (four to iohexol, three iodixanol and two to iomeprol). In cases with a negative skin test to all CM tested (N = 74), provocation test was carried out with the culprit CM if known, being positive in three cases: one to iodixanol, one to iomeprol and one to iodixanol, iohexol plus iomeprol. In total, 11 patients with a negative ST refused to undergo a provocation test, resulting in a negative predictive value to immediate hypersensitivity reactions of 95.26%. Eight (8.9%) cases were confirmed as having IHR, 5 (62.5%) by ST and 3 (37.5%) by provocation test. Five from those confirmed as IHR (62.5%) had a positive BAT.

The rate of a positive skin test in the study of Sesé (2016) was 13.5% (95% CI 4 to 29%) and increased to 20% (95% CI 4 to 48%) for patients who consulted during the year after the HSR. Among the 32 patients with negative skin test results, 31 were challenged successfully, 15 with the culprit ICM. One grade I reaction occurred 2 h after challenge (generalized pruritus, erythema, and eyelid oedema lasting < 1 h) and was considered a positive intravenous challenge result. At 2 h after provocation test, two patients reported generalized and isolated pruritus that regressed with antihistamine therapy and was not considered a positive IPT result. None of five patients with positive skin test to ICM were re- exposed to contrast media during radiologic examination, positive predictive could not be calculated. For an immediate HSR to ICM, the negative predictive value for skin tests with low dose was 80% (95% CI 44 to 97%).

2. *Diagnostic characteristics of cutaneous tests for **nonimmediate** hypersensitivity reactions*

In Torres (2012), 34 subjects (21.1%) developed a positive delayed reading of the intradermal tests (13 at 1/10 dilution and 29 undiluted). Of these, 27 were skin-test positive to just one CM, 6 to two CM and 1 to three. The immediate reading of the intradermal tests was negative in all cases. The skin test was positive to iomeprol in 21 cases (50%), to iodixanol in 7 (16.7%), to iobitridol in 5 (11.9%), to ioxaglate in 4 (9.5%), to iohexol in 3 (7.1%) and to iopromide in 1 (2.4%). In the 34 cases with a positive intradermal test, 10 also had a positive patch test. No positive patch tests were detected in the patients with negative intradermal results. In the patients with a negative skin test to all the CM tested (N = 127), a provocation test was carried out with the CM involved. Provocation test was positive in 44 cases (34.6%), 19 to one CM and 3 to two CM. Thirty-eight cases (76%) were positive to iodixanol, 8 (16%) to iomeprol and 4 (8%) to iohexol. The time interval between administration and symptom development was: 1 to 6 h (13 cases), 7 to 12 h (27 cases), 13 to 24 h (68 cases), 25 to 48 h (41 cases) and > 48 h (12 cases).

3. *Other tests*

Meucci (2020) (n=98) reported NPV for skin tests of 96.2% for immediate hypersensitivity reactions and 58.8% for delayed hypersensitivity reactions, in favour of immediate hypersensitivity reactions (p<0.0001) when administering ICM different than the culprit. Furthermore, the NPV for the drug provocation test with culprit ICM was 50%. The NPV for the total diagnostic protocol was 92.3%, for patients undergoing a drug provocation test and exposure to the same ICM in a real-life setting.

4. *Hypersensitivity reactions to gadolinium-based contrast agents (GBCA)*

Results not reported.

Quality of evidence

The level of evidence towards the outcome measure **diagnostic characteristics of cutaneous tests for HSR** was graded as very low due to high risk of bias (see Risk of Bias table in the Supplement 'Appendices to modules', downgraded by two points) and low number of patients (imprecision downgraded by one point).

## Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: What is the diagnostic value of skin testing for hypersensitivity reactions to contrast media?

**P** (Patient category) Patients with hypersensitivity reactions after radiological examinations with contrast media.
**I** (Intervention) Cutaneous tests: skin test, patch test (PT), intradermal test (IDT), skin prick test (SPT) or scratch test.
**C** (comparison) Clinical diagnosis of hypersensitivity reaction after contrast administration.
**R** (Reference) Drug provocation test.

**O** (outcome) Correctly confirmed diagnosis of hypersensitivity reaction to contrast media (sensitivity, specificity, area under the curve, positive predictive value, negative predictive value).

Relevant outcome measures
The working group considered sensitivity and specificity critical outcome measures for the decision-making process; and considered the area under the curve and the positive and negative predictive values important outcome measures.

Search and select (Methods)
On April 22nd, 2021, a systematic search was conducted in the databases Embase (embase.com) and Medline (OVID) from 2017 onwards, using relevant key words for systematic reviews, RCT's, observational studies and other study designs about
hypersensitivity reactions after contrast media. Specifically, the value of serum and/or urine tests, either skin tests or prophylactic measures were sought. The literature search yielded 400 unique references.

Studies were selected based on the following criteria:

- Adult patients with ≥1 hypersensitivity reaction(s) to contrast media
- Evaluation of diagnostic properties of cutaneous tests to contrast media
- Application of a provocation test to confirm results of cutaneous testing
- Reports predefined outcome measures: sensitivity, specificity, area under the curve, positive predictive value, negative predictive value
- No reports of case series or exploratory findings (n ≥ 10)

Based on title and abstract, a total of twenty-one studies were selected. After examination of full text, a total of eighteen studies were excluded and three new studies to the earlier synthesis of 2017 were included in the literature summary. Reason for exclusion is reported in Table of excluded studies which can be found in the supplementary document Appendices to modules.

Three studies were added to the literature analysis of 2017. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables. Two studies (Kim, 2017; Schrijvers, 2018) did not fulfil the predefined selection criteria but described the negative predictive values of IDT and skin tests in patients who had a hypersensitivity reaction after CM administration. Since these studies did not fulfil the selection criteria and did not include a comparison to a reference test, only descriptive data of these studies was shown, and evidence tables and risk of bias tables of these studies are not included.

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

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# Risicofactoren voor hypersensitiviteitsreacties na CM

## Uitgangsvraag

Welke patiënten hebben een verhoogd risico op hypersensitiviteitsreacties na contrastmiddeltoediening?

## Aanbeveling

Beschouw alleen een eerdere hypersensitiviteitsreactie als een relevante risicofactor voor het ontwikkelen van een nieuwe hypersensitiviteitsreactie.

## Overwegingen

Although various potential risk factors were identified in the five studies mentioned above, there are several limitations to be addressed.

First, all reported data solely address iodine-based contrast media (ICM). It is not clear whether these findings can be extrapolated to gadolinium-based contrast agents (GBCA).

Second, hypersensitivity reactions are generally diagnosed on clinical symptoms only and often in retrospect. Therefore, it is likely that the outcome group in many studies consists of a mixture of true HSR and other, nonimmune-mediated adverse events caused by severe physiological effects, chemotoxic effects and/or anxiety (Lalli, 1974). The increased odds ratio reported by Cha, 2019 for hyperthyroidism suggests inclusion of other reactions, since this risk factor was not reported by any other study and is suggestive of iodine-induced hyperthyroidism, which may present with clinical features with a certain overlap to mild hypersensitivity reactions.

Third, the hypersensitivity reactions are analysed together, while stratification for immediate vs nonimmediate reactions and based on severity would be preferred. Since immediate (IgE- or non-IgE-mediated mast cell activation) and nonimmediate (T-cell mediated) HSR are pathophysiological distinct, we assume that risk factors may be different as well. For example, a genetic predisposition is possible for T-cell mediated nonimmediate HSR since different HLA types may predispose for certain drug hypersensitivity reactions. Since mast cells belong to the innate immune system, it is from a pathophysiological standpoint hard to understand why there would be an increased risk in certain families, except for rare forms of familial mastocytosis.

Moreover, except for Kim, 2017, none of the studies stratified outcomes according to severity of the HSR. This is important, since identifying risk factors for severe reactions such as anaphylaxis has the highest clinical relevance. Cha, 2019 and colleagues reported that 968 (68.8%) of the 1433 patients with an ICM-related HSR recovered spontaneously; identifying a risk factor for a self-limiting reaction has little clinical relevance and will not lead to adaption of protocols. Only the study by Kim (2017) reported outcomes separately for anaphylaxis. Since anaphylaxis is rare, it is difficult to gain sufficient power for statistical analyses.

Fourth, the robustness of findings depends on validation by other studies. A previous reaction to CM has been reported by several studies and is therefore more likely to be relevant than hyperthyroidism or a positive family history.

Fifth, the absolute OR or RR adds to the clinical relevance. Kim et al. (Kim, 2017) proposed risk factor "body weight" (which is not clearly mentioned in the results, table 2 suggests that a higher body weight may be a risk factor but remains unclear) is a risk factor for (all) immediate HSR. With an OR of 1.02 this is of no clinical relevance, aside from the other limitations. Overall, the highest odds ratios were noted for previous CM reactions.

As mentioned before, it is uncertain whether previous reactions would be a risk factor for GBCA as well since literature on GBCA is scarce. A meta-analysis of nine studies in which immediate reactions to GBCA were recorded from a total of 716,978 GBCA administrations met the criteria for inclusion. The overall and severe rates of GBCA allergic-like adverse events were 9.2 and 0.52 per 10,000 administrations, respectively: 539 of 662 (81%) were mild, 86 (13%) were moderate, and 37 (6%) were severe reactions. The nonionic linear chelate gadodiamide had the lowest rate of reactions, at 1.5 per 10,000 administrations, which was significantly less than that of linear ionic GBCAs at 8.3 and nonionic macrocyclic GBCAs at 16 per 10,000 administrations. GBCAs known to be associated with protein-binding (like gadobenate) had a higher rate of reactions, at 17 per 10,000 administrations compared with the same chelate classification without protein binding, at 5.2 per 10,000 administrations (Behzadi, 2018).

A large retrospective study in children and adults studied all intravenous GBCA injections performed at a single institution. A total of 158,100 patients received 281,945 GBCA injections (140,645 gadodiamide, 94,109 gadobutrol, 39,138 gadobenate, and 8,053 gadoterate). At multivariate analysis, gadobenate or gadobutrol had higher rates of allergic- like reactions compared with gadodiamide (gadobenate: odds ratio (OR), 3.9; gadobutrol: OR, 2.3) or gadoterate (gadobenate: OR, 4.8; gadobutrol: OR, 2.8). Six severe allergic-like reactions (three gadobutrol, three gadobenate) occurred requiring hospitalization. Patient age ($P = 0.025$ to $< 0.001$), sex ($P < 0.001$), location ($P = 0.006$), and MRI type ($P = 0.003$ and $P = 0.006$) were associated with acute reactions (McDonald, 2019).

Thus, both studies suggest that the type of GBCA may be a relevant risk factor, but do not take the severity of the reaction into account. The importance is limited as the total reaction rate is very low and the large majority of those reactions are mild and self-limiting.

Taken together, a previous reaction to CM appears to be the only clinically relevant risk factor for developing a new hypersensitivity reaction based on the currently available literature. It is plausible that the same holds true for GBCA, although there is currently not enough literature available to solidly confirm this.

In the ACR Manual on Contrast Media v.2021 (ACR, 2022) and the ESUR v10 guidelines (ESUR 2018), the most significant risk factor for increased risk of hypersensitivity reactions remains a documented history of a previous hypersensitivity reaction to a contrast medium. Patients with atopy/bronchial asthma or multiple allergies could not be established as a consistent risk factor (Chen, 2015; Jung, 2016).

### Recommendations

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| Only consider a previous hypersensitivity reaction after contrast media administration a relevant risk factor for developing a new hypersensitivity reaction. |

## Onderbouwing

### Achtergrond

Like virtually any drug or substance, all types of contrast media have the potential to elicit a hypersensitivity reaction (HSR) (see also Introduction). Ideally, such adverse events are prevented, but this is difficult and to date not realistic. Identifying patients with an increased risk of developing HSRs would be a first step. General risk factors for an aggravated HSR include severe asthma, systemic mastocytosis, or the use of medication such as ß-blockers. In addition, patient in need of contrast media (CM) administration may report HSRs to a previous CM administration. This can involve objective signs or symptoms that fit well with a hypersensitivity reaction. However, in many cases other complaints are reported, such as hyperventilation, vasovagal reactions, or stress-induced responses such as throat tightness or panic attacks. These may not fit accurately with a hypersensitivity reaction to CM and thus may affect the risk of a HSR at repeated exposure.

All types of contrast media will be evaluated: iodine-based, gadolinium-based, and microbubble ultrasound CM. Also, all types of administration routes will be covered, intravascular (intravenous or intra-arterial), oral and rectal, intracavitary (joints or bladder), and intraductal (bile or pancreatic ducts). Nonvascular CM administration has already been summarized in Safe Use of Contrast Media, part 2.

### Conclusies / Summary of Findings

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| **Low GRADE** | The following factors were associated with an increased risk of adverse drug reaction in patients undergoing coronary angiography or percutaneous coronary intervention and receiving iopromide contrast:<br><br>• Age < 50 years<br>• No premedication with corticosteroids<br>• Contrast dose < 100mL<br>• No pre-procedural hydration<br>• Left main coronary disease<br>• Previous ADR to contrast<br><br>Allergic constitution, asthma and sex were not independently associated with the risk of developing an adverse reaction.<br><br>*Chen, 2015* |

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| **Low GRADE** | The following factors were associated with an increased risk for developing a **second** acute allergic-like adverse reaction in patients with a history of a hypersensitivity reaction after low-osmolality contrast administration, who were undergoing another enhanced computed tomography with low- osmolality contrast medium and receiving premedication:<br><br>• Younger age<br>• Previous severe reaction<br>• No corticosteroid premedication<br><br>The following factors were not independently associated with the risk of acute allergic-like adverse reactions: sex, bronchial asthma, allergic rhinitis, chronic urticaria, food allergy, other drug allergy, H2-antihistamines premedication.<br><br>*Jung, 2016* |

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| **Low GRADE** | The following factors were associated with increased risk of immediate HSR:<br><br>• Types of RCMs (compared to iobitridol)<br>  ◦ Iohexol (OR: 1.36, 95% CI:1.08 to 1.72)<br>  ◦ Iopamidol (OR: 1.59, 95% CI: 1.28 to 1.98)<br>  ◦ Iopromide (OR: 2.72, 95% CI: 2.17 to 3.41)<br>• Multiple CT (OR: 2.13, 95% CI: 1.89 to 2.38)<br>• Female (OR: 1.51, 95% CI: 1.36 to 1.67)<br>• Age 20 to 50 (OR: 1.55, 95% CI: 1.01 to 2.37)<br>• Body weight (OR: 1.02, 95% CI: 1.01 to 1.02)<br><br>The following factors were associated with increased risk of anaphylaxis:<br><br>• Iopromide (OR: 6.24, 95% CI: 1.32 to 29.44)<br>• Multiple CT (OR: 3.26, 95% CI: 1.81 to 5.86)<br><br>The following factors were not independently associated with the risk of anaphylaxis: Iohexol, Iopamidol, sex, age, and body weight.<br><br>*Kim, 2017* |

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| **Low GRADE** | The following factors were associated with increased risk of occurrence and recurrence of ICM-related HSRs:<br><br>• Hyperthyroidism (OR: 4.00, 95% CI: 1.4 to 12.1)<br>• Drug allergy (OR: 5.2, 95% CI: 2.8 to 9.7)<br>• Asthma (OR: 2.3, 95% CI: 1.1 to 4.9)<br>• Other allergic disease (OR: 9.5, 95% CI: 4.1 to 22.1)<br>• Past history of ICM exposure<br><br>o HSR to ICM (OR: 56.3, 95% CI: 20 to 151)<br><br>• Family history<br><br>o HSR to ICM (OR: 11.1, 95% CI: 1.4 to 85.9)<br><br>The following factor were associated with decreased risk of occurrence and recurrence of ICM related HSRs:<br><br>• Past history of ICM exposure<br>◦ No HSR to ICM usage (OR: 0.7, 95% CI: 0.6 to 0.8)<br><br>*Cha, 2019* |

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| **Low GRADE** | The following factors were associated with an increased risk for developing a **second** hypersensitivity reaction in patients with a history of a moderate or severe hypersensitivity reaction after low-osmolality contrast administration, who were undergoing another enhanced computed tomography with low- osmolality contrast medium and receiving premedication:<br><br>• Younger age<br>• Diabetes mellitus<br>• Chronic urticaria<br>• Drug allergy<br>• Not changing the iodinated contrast medium<br>• Initial hypersensitivity reaction was severe<br><br>The following factors were not independently associated with the risk of developing a recurrent hypersensitivity reaction: sex, use of premedication.<br><br>*Park, 2017* |

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| **Low GRADE** | The following factors were associated with increased risk of immediate HSRs:<br><br>• Female (RR: 1.22 (95% CI: 1.04 to 1.43)<br>• History of acute hypersensitivity to iodinated contrast material (RR: 10.4, 95% CI: 4.51 to 24.2)<br>• Contrast media used for study CT<br><br>o Iomeprol (RR: 4.48, 95% CI: 3.09 to 6.48)<br><br>• Iodine concentration for study CT<br><br>o 350 mg I/mL (RR: 4.66, 95% CI: 2.92 to 7.42)<br>o ≥370 mg I/mL (RR: 2.83, 95% CI: 2.13 to 3.77)<br><br>The following factor were associated with **decreased** risk of acute HSRs:<br><br>• Age (RR: 0.98, 95% CI: 0.97 to 0.98)<br>• Premedication for study CT<br>  ◦ Antihistamine alone (RR: 0.39, 95% CI: 0.17 to 0.9)<br>  ◦ Steroid with or without antihistamine (RR: 0.37, 95% CI: 0.16 to 0.89)<br>• Type of CT examination<br>  ◦ Multiphase (RR:0.41, 95% CI: 0.32 to 0.52)<br><br>*Park, 2019* |

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| **Low GRADE** | The following factors were associated with increased risk of immediate and nonimmediate HSR:<br><br>• Immediate HSR: Previous IA exposure (OR: 2.92, 95% CI: 1.22 to 6.96)<br>• Nonimmediate HSR: Iodixanol (OR: 1.61, 95% CI: 1.07 to 2.43)<br><br>*Sohn, 2019* |

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| **Low GRADE** | The following factors were associated with increased risk of HSR:<br>• Age<br>  ◦ 50-<65 (OR: 1.67, 95% CI: 1.38 to 2.02)<br>  ◦ 18-<50 (OR: 2.16, 95% CI: 1.78 to 2.62)<br>• Female (OR: 1.16, 95% CI: 1.01 to 1.34)<br>• Diabetes mellitus (OR: 1.54, 95% CI: 1.19 to 2.00)<br>• Allergy (OR: 3.61, 95% CI: 2.84 to 4.59)<br>• Asthma (OR: 2.14, 95% CI: 1.26 to 3.62)<br>• Previous contrast media reaction (OR: 4.31, 95% CI: 2.75 to 6.75)<br>• Other concomitant disease: (OR: 1.42, 95% CI: 1.19 to 1.70)<br>• Geographic region: Asia (OR: 1.80, 95% CI: 1.54 to 2.11)<br>• Dose of iodine in CM<br>  ◦ >20–40 g (OR: 1.24, 95% CI: 1.01 to 1.51)<br>• Iopromide concentration<br>  ◦ Iopromide 370 (OR: 1.31, 95% CI: 1.12 to 1.54)<br><br>The following factor was associated with increased risk of HSR:<br>• IA Injection route (OR: 0.23, 95% CI: 0.16 to 0.32) |

## Samenvatting literatuur

Description of studies

A total of 3 studies from Safe Use of Contrast Media, part 2 described factors independently related to the risk of hypersensitivity reactions after contrast administration. All studies presented multivariate models, but no internal or external validation of these models, or the results of application of these models in clinical practice.

A total of five studies described factors independently related to the risk of hypersensitivity reactions after contrast media administration. All studies presented multivariate models, but no internal or external validation of these models, or the results of application of these models in clinical practice.

Cha (2019) in a prospective cohort study described the risk factors associated with iodinated contrast media (ICM) -related hypersensitivity reactions in 196081 patients who underwent contrast-enhanced CT examinations from seven tertiary referral hospitals in Korea.

Chen (2015) described the risk factors associated with adverse reactions (occurring within 1 hour after contrast administration) in 17,513 patients who were administered iopromide (300 or 370 mgI/mL) contrast during coronary angiography or Percutaneous Coronary Intervention (PCI). All patients (not high-risk patients only) were included in this multicentre (63 centres in China) study.

Endrikat (2020) in a case control study described the risk factors associated with hypersensitivity reactions to iopromide after intra-arterial administration and intravenous
(IV) administration in 133,331 patients undergoing angiographic procedures (mostly cardio angiography) or contrast-enhanced CT. Four observational studies were pooled. Almost half of the study population (48.1%) was from Europe, and one quarter each from China (27.6%) and other Asia countries (24.1%). Hypersensitivity reactions were recorded for 822 patients, and 132,509 patients served as controls.

Kim (2017) in a retrospective cohort described the risk factors associated with immediate adverse drug reactions (ADRs) occurred within 1 h after administration of radiocontrast media (RCMs) in 1969 immediate ADRs from 286,087 examinations of 142,099 patients who underwent contrast-enhanced computed tomography (CT) examinations.

Jung (2016) described risk factors for developing a hypersensitivity reaction after re- administration of low-osmolality iodinated contrast medium for enhanced computed tomography in 322 patients with a history of hypersensitivity reactions after low-osmolality contrast administration. A total of 219 (68%) of the patients had a mild reaction, while 82 (26%) had a moderate reaction, and 21 (7%) a severe reaction in their history. Premedication was decided on an individual basis by clinicians and could consist of oral and/or intravenous H1-antihistamines, H2-antihistamins and corticosteroids.

Park (2017) described risk factors for developing a hypersensitivity reaction after administration of low-osmolar iodinated contrast medium for enhanced computed tomography in 150 patients with a history of moderate 130 (87%) to severe 20 (13%) hypersensitivity reactions after contrast administration in 328 instances of re-exposure. Patients received antihistamines and/or corticosteroids as pre-medication, the exact premedication was decided on an individual basis.

Park (2019) in a retrospective cohort described the risk factors associated with non-ionic ICM related hypersensitivity reactions in 21,947 adults during the control period and 26,491 patients during intervention period undergoing contrast–enhanced abdominal CT. Compared with CT during the control period, CT during the intervention period involved a reduced dose of contrast media achieved by lowering the CT tube voltage. Antihistamines alone were used for mild reactions, and steroids were used for moderate or severe reactions as pre-medication.

Sohn (2019) in a prospective cohort study described the risk factors associated with immediate and delayed coronary angiography (CAG)-induced ICM hypersensitivity in 714 patients who underwent CAG using intra-arterial (IA) administration of ICM including ioversol, a low-osmolar non-ionic monomer, and iodixanol, an iso-osmolar non-ionic dimer.

Results

Cha (2019) reported that the overall prevalence of HSRs was 0.73% (1,433 of 196,081), while severe reactions occurred in 0.01% (17 of 196,081). In terms of severity, 83.2% of the events were classified as mild HSRs, with a relative prevalence of 83.2% (overall 0.61%; 1,192 of 196,081); 15.6% as moderate HSRs (overall 0.11%; 224 of 196,081); and 1.2% as severe HSRs (overall 0.01%; 17 of 196,081).

The following factors were associated with increased risk of occurrence and recurrence of ICM related HSRs:

- Hyperthyroidism (OR: 4.00, 95% CI: 1.4 to 12.1)
- Drug allergy (OR: 5.2, 95% CI: 2.8 to 9.7)
- Asthma (OR: 2.3, 95% CI: 1.1 to 4.9)
- Other allergic disease (OR: 9.5, 95% CI: 4.1 to 22.1)
- Past history of ICM exposure
    - HSR to ICM (OR: 56.3, 95% CI: 20 to 151)
- Family history
    - HSR to ICM (OR: 11.1, 95% CI: 1.4 to 85.9)

The following factor was associated with decreased risk of occurrence and recurrence of ICM related HSRs:

- Past history of ICM exposure
    - No HSR to ICM usage (OR: 0.7, 95% CI: 0.6 to 0.8)

Chen (2015) reported that acute adverse drug reactions (ADRs) occurred in 66/17,513 (0.38%) patients undergoing iopromide (300 or 370 mgI/mL) administration during coronary angiography or Percutaneous Coronary Intervention (PCI), out of which 2 ADRs (0.01%) were severe. Most ADRs manifested as nausea vomiting (0.22%) and rash (0.09%).

The following factors were associated with risk of ADR:

- Age 50 to 69 versus age < 50 (OR: 0.48, 95% CI: 0.27 to 0.85)
- Premedication with corticosteroids (OR: 0.41, 95% CI: 0.18 to 0.97)
- Contrast dose ≥ 100mL (OR 0.50, 95% CI 0.30 to 0.82)
- Pre-procedural hydration (OR: 0.11, 95% CI: 0.04 to 0.33)
- Left main coronary disease (OR: 2.27, 95% CI: 1.15 to 4.48)
- Previous ADR to contrast (OR: 9.30, 95% CI: 1.10 to78.84)

Allergic constitution, asthma and sex were not independently associated with the risk of developing an adverse reaction.

Endrikat (2020) reported HSR in 822/133,331 patients (0.62%). The most frequent hypersensitivity reactions were skin reactions (erythema, urticaria, rash), reported in 508 patients (0.38%), followed by pruritus (n = 294; 0.22%), cough/ sneezing (n = 151; 0.11%), and dyspnoea/bronchospasm (n = 105; 0.08%). Hypersensitivity reactions were significantly more frequently recorded after IV than after IA administration, 0.7% versus 0.2%, respectively. Their follow-up study (Endrikat, 2022) reported a decreased risk of HSR in elderly > 65 years, at least when iopromide was used.

The following factors were associated with increased risk of HSR:

- Age
    - 50-<65 (OR: 1.67, 95% CI: 1.38 to 2.02)
    - 18-<50 (OR: 2.16, 95% CI: 1.78 to 2.62)

- Female (OR: 1.16, 95% CI: 1.01 to 1.34)
- Diabetes mellitus (OR: 1.54, 95% CI: 1.19 to 2.00)
- Allergy (OR: 3.61, 95% CI: 2.84 to 4.59)
- Asthma (OR: 2.14, 95% CI: 1.26 to 3.62)
- Previous contrast media reaction (OR: 4.31, 95% CI: 2.75 to 6.75)
- Other concomitant disease: (OR: 1.42, 95% CI: 1.19 to 1.70)
- Geographic region: Asia (OR: 1.80, 95% CI: 1.54 to 2.11)
- Dose of iodine in CM
    - >20–40 g (OR: 1.24, 95% CI: 1.01 to 1.51)
- Iopromide concentration
    - Iopromide 370 (OR: 1.31, 95% CI: 1.12 to 1.54)

The following factor were associated with decreased risk of HSR:

- IA Injection route (OR: 0.23, 95% CI: 0.16 to 0.32)
- >65 (OR: 0.51 95% CI: 0.43 to 0.61)

Jung (2016) described that 47/322 (15%) of the patients experienced a recurrence of an allergic reaction after low-osmolality iodinated contrast medium administration for computed tomography, despite premedication.

The following factors were associated with an increased risk for developing this second acute allergic-like adverse reaction:

- Age (OR: 0.97, 95% CI: 0.94 to 0.99).
- Previous severe reaction (OR: 8.88, 95% CI: 2.11 to 37.42).
- Not using corticosteroid premedication (OR: 0.28, 95% CI: 0.10 to 0.78) - people that used corticosteroid medications had a lower risk to experience an allergic reaction.

The following factors were not independently associated with the risk of acute allergic-like adverse reactions: sex, bronchial asthma, allergic rhinitis, chronic urticaria, food allergy, other drug allergy, H2-antihistamines premedication.

Kim (2017) reported that immediate adverse drug reactions (ADRs) occurred in 1969 cases of ADR (0.69%) among 286,087 cases in 142,099 patients who underwent contrasted CT examinations. Rash (85.3%) and itching sensation (59.8%) were the most frequent symptoms. Among these immediate ADRs, 68 cases were classified as anaphylaxis (0.024%). They found that iopromide had the highest incidence of immediate ADRs (1.03%) and was followed by iopamidol (0.67%), iohexol (0.64%), and iobitridol (0.34%). In cases of anaphylaxis, iopromide also showed the highest incidence (0.041%), followed by iopamidol (0.023%), iohexol (0.018%), and iobitridol (0.012%).

The following factors were associated with increased risk of immediate ADR:

- Types of RCMs (compared to iobitridol)
    - Iohexol (OR: 1.36, 95% CI:1.08 to 1.72)
    - Iopamidol (OR: 1.59, 95% CI: 1.28 to 1.98)

    - Iopromide (OR: 2.72, 95% CI: 2.17 to 3.41)
- Multiple CT examinations (OR: 2.13, 95% CI: 1.89 to 2.38)
- Female sex (OR: 1.51, 95% CI: 1.36 to 1.67)
- Age 20 to 50 (OR: 1.55, 95% CI: 1.01 to 2.37)
- Body weight (OR: 1.02, 95% CI: 1.01 to 1.02)

The following factors were associated with increased risk of anaphylaxis:

- Iopromide (OR: 6.24, 95% CI: 1.32 to 29.44)
- Multiple CT examinations (OR: 3.26, 95% CI: 1.81 to 5.86)

The following factors were not independently associated with the risk of anaphylaxis: iohexol, iopamidol, sex, age, and body weight.

Park (2017) reported that a recurrence of hypersensitivity reactions after contrast exposure occurred in 64/328 (20%) of the instances of re-exposure to low-osmolar iodinated contrast in patients with a history of moderate or severe reactions.

The following factors were associated with an increased risk for developing this second hypersensitivity reaction:

- Age (OR: 0.97, 95% CI 0.94 to 0.99);
- Diabetes mellitus (OR: 6.49, 95% CI: 2.38 to 17.71);
- Chronic urticaria (OR: 7.61, 95% CI: 1.63 to 35.59);
- Drug allergy (OR: 3.69, 95% CI: 1.18 to 11.56);
- Changing the iodinated contrast medium (OR: 0.33, 95% CI: 0.17 to 0.64);
- Initial hypersensitivity reaction was severe (OR: 2.67, 95% CI: 1.05 to 6.79).

The following factors were not independently associated with the risk of developing a recurrent hypersensitivity reaction: sex, use of premedication.

Park (2019) reported the following factors associated with increased risk of acute HSRs:

- Female (RR: 1.22 (95% CI: 1.04 to 1.43)
- History of acute hypersensitivity to iodinated contrast material (RR: 10.4, 95% CI: 4.51 to 24.2)
- Contrast media used for study CT
    - Iomeprol (RR: 4.48, 95% CI: 3.09 to 6.48)
- Iodine concentration for study CT
    - 350 mg I/mL (RR: 4.66, 95% CI: 2.92 to 7.42)
    - ≥370 mg I/mL (RR: 2.83, 95% CI: 2.13 to 3.77)

The following factors were associated with decreased risk of acute HSRs:

- Age (RR: 0.98, 95% CI: 0.97 to 0.98)

- Premedication for study CT
    - Antihistamines alone (RR: 0.39, 95% CI: 0.17 to 0.9)
    - Steroid with or without antihistamines (RR: 0.37, 95% CI: 0.16 to 0.89)
- Type of CT examination
    - Multiphase (RR: 0.41, 95% CI: 0.32 to 0.52)

Sohn (2019) reported 26 of 714 (3.6%) patients with immediate HSR and 108 of 714 (15.1%) with non-immediate HSR after IA contrast administration. With regard to severity, the proportion of immediate HSR grades 1, 2, and 3 was 57.7%, 38.5%, and 3.8%, respectively,
whereas that of non-immediate HSR grades 1, 2, and 3 was 85.2%, 13.9%, and 0.9%, respectively.

The following factors were associated with increased risk of immediate and nonimmediate HSR:

- Immediate HSR: Previous IA exposure (OR: 2.92, 95% CI: 1.22 to 6.96)
- Nonimmediate HSR: Iodixanol (OR: 1.61, 95% CI: 1.07 to 2.43)

Level of evidence of the literature
For all included patient populations, the quality of certainty of evidence for the outcome hypersensitivity reaction was downgraded from high to low by two points, due to risk of bias and indirectness: the prognostic factors were identified, but the prognostics model was not validated internally and externally. The value of the applicability of the multivariate models in a clinical decision-making process was not evaluated. The study sample in the primary studies do not accurately reflect the review question.

## Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: *Which factors are related to an increased risk of developing hypersensitivity reactions after contrast administration?*

**P:** (Patients) Patients undergoing radiological examinations with contrast media
**I:** (Intervention) Presence of prognostic factors
**C:** (Control) Absence of prognostic factors
**O:** (Outcome) Allergic reactions to contrast media, hypersensitivity reaction, type I / type IV, severe allergic reaction

Relevant outcome measures
The working group considered allergic / hypersensitivity reactions to contrast media critical outcome measures for the decision-making process.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until April 22nd, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 400 hits.

Studies were selected based on the following criteria:

- Adult patients undergoing radiological examinations with contrast media.
- Evaluation or identification of factors associated with an increased risk of hypersensitivity reactions after contrast administration. These factors could be treatment related, or patient related. Studies were only included when the identified risk factors were corrected for confounders (multivariate models).
- Reports predefined outcome measure: hypersensitivity reactions.
- No reports of case series or exploratory findings (n ≥ 10).

Based on title and abstract a total of forty-seven studies were selected. After examination of full text, a total of forty-two studies were excluded and five studies were included in the literature summary. Reason for exclusion is reported in the exclusion table.

Five studies were included for the research question regarding the identification of factors associated with an increased risk of hypersensitivity reactions after contrast administration. 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 : 28-11-2022

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

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# Profylactische maatregelen om hypersensitiviteitsreacties na CM te voorkomen

## Uitgangsvraag

Welke profylactische maatregelen zouden moeten worden genomen bij patiënten met een verhoogd risico op hypersensitiviteitsreacties na contrastmiddel(CM)-toediening?

Deze vraag bevat de volgende categorieën:

1. Patiënten met voorgaande (acute) hypersensitiviteitsreacties na jodiumhoudend CM of gadoliniumhoudend CM
2. Patiënten met voorgaande doorbraakreactie na CM
3. Patiënten met een voorgaande hypersensitiviteitsreactie na meerdere CM
4. Patiënten met een voorgaande niet-acute (vertraagde) hypersensitiviteitsreactie na jodiumhoudend CM of gadoliniumhoudend CM
5. Kruisreactiviteit tussen CM
6. Documentatie van hypersensitiviteitsreacties

## Aanbeveling

Bij alle patiënten met een (gedocumenteerde) geschiedenis van een hypersensitiviteitsreactie op een jodiumhoudend contrastmiddel of een gadoliniumhoudend contrastmiddel, overweeg een alternatieve beeldvormingstechniek. Wanneer dit niet mogelijk is, overweeg om onderzoek zonder contrastmiddel uit te voeren, maar alleen als dit een acceptabele reductie in diagnostische kwaliteit oplevert.

<u>1. Patiënten met voorgaande (acute) hypersensitiviteitsreacties na jodiumhoudend contrastmiddel of gadoliniumhoudend contrastmiddel</u>

Bij patiënten met een (gedocumenteerde) geschiedenis van een **milde acute** hypersensitiviteitsreactie door jodiumhoudend contrastmiddel of gadoliniumhoudende contrastmiddel:

- Behandel deze patiënten als elke andere patiënt, aangezien er geen risico is op het ontwikkelen van een matige of ernstige overgevoeligheidsreactie.

Bij patiënten met een (gedocumenteerde) geschiedenis van een **matige tot ernstige acute** overgevoeligheidsreactie door jodiumhoudend contrastmiddel of gadoliniumhoudende contrastmiddel:

- Stel het onderzoek uit en verwijs naar een allergoloog.

Als er geen tijd is om de patiënt naar een allergoloog te verwijzen:

- Kies een ander jodiumhoudend contrastmiddel of gadoliniumhoudend contrastmiddel als het contrastmiddel dat de reactie veroorzaakte bekend is*
- Overweeg om een test te doen door eerst 10% van het contrastmiddel te geven en de patiënt

>15 minuten te observeren: vooral bij ernstige reacties en wanneer het contrastmiddel dat de reactie veroorzaakte onbekend is

- Observeer de patiënt ≥ 30 min met behoud van intraveneuze toegang
- Wees alert op een nieuwe overgevoeligheidsreactie

*Zie ook flow charts

2. Patiënten met voorgaande doorbraakreactie na contrastmiddelen

Verwijs patiënten met een doorbraak overgevoeligheidsreactie op jodiumhoudend contrastmiddel of gadoliniumhoudend contrastmiddel altijd naar een allergoloog voor huidtesten met verschillende jodiumhoudende contrastmiddelen en gadoliniumhoudende contrastmiddelen.

*Zie ook flow charts

3. Patiënten met een voorgaande hypersensitiviteitsreactie na meerdere contrastmiddelen

Verwijs patiënten met een overgevoeligheidsreactie na meerdere jodiumhoudende contrastmiddelen of gadoliniumhoudende contrastmiddelen (ofwel 2 of meer jodiumhoudende contrastmiddelen, ofwel 2 of meer gadoliniumhoudende contrastmiddelen, ofwel een jodiumhoudend contrastmiddel én een gadoliniumhoudend contrastmiddel) altijd naar een allergoloog. Pas daarnaast dezelfde principes als hierboven omschreven toe.

*Zie ook flow charts

4. Patiënten met een voorgaande niet-acute (vertraagde) hypersensitiviteitsreactie na jodiumhoudend contrastmiddel of gadoliniumhoudend contrastmiddel

Bij patiënten met (verdenking op) een eerdere ernstige niet-acute cutane overgevoeligheidsreactie waarbij alarmsymptomen** aanwezig waren:

- Geef **geen** jodiumhoudend contrastmiddel of gadoliniumhoudend contrastmiddel
- Verwijs de patiënt direct naar een allergoloog.

Bij patiënten met een geschiedenis van een milde-matige niet-acute cutane overgevoeligheidsreactie waarbij alarmsymptomen** ontbraken:

- Kies een ander jodiumhoudend contrastmiddel of gadoliniumhoudend contrastmiddel als het contrastmiddel dat de reactie veroorzaakte bekend is*
- Geef instructies aan de patiënt als de reactie opnieuw optreedt om foto's van de huidlaesies te maken en naar de radiologie-afdeling te sturen voor beoordeling

*Zie ook flow charts

5. Kruisreactiviteit tussen contrastmiddelen

Kruisreactiviteit is het meest relevant bij *allergische* hypersensitiviteitsreacties. Er is een hogere kans op kruisreactiviteit bij:

- Jodiumhoudend contrastmiddel met een *N*-(2,3 hydroxypropyl)-carbamoyl zijketen
- Macrocyclisch gadolinium-houdend contrastmiddel

De allergoloog bepaalt door middel van huidtesten met verschillende jodiumhoudende contrastmiddelen en gadoliniumhoudende contrastmiddelen:

- De oorzaak van de allergische reactie
- Kruisreactiviteit tussen verschillende contrastmiddelen
- Suggesties voor veilige alternatieve contrastmiddelen

6. Documentatie van hypersensitiviteitsreacties

De arts die verantwoordelijk is voor de toediening van het contrastmiddel is ook verantwoordelijk voor accurate documentatie van de hypersensitiviteitsreactie in het verslag van de beeldvorming.

De arts die verantwoordelijk is voor de toediening van het contrastmiddel of de allergoloog is ook verantwoordelijk voor accurate documentatie van de hypersensitiviteitsreactie in het elektronisch patiëntendossier.

Documenteer altijd op naam van het specifieke contrastmiddel en dit moet alleen gedaan worden door artsen of allergologen met ervaring op het gebied van contrastmiddelen.

Registreer het volgende na elke overgevoeligheidsreactie op contrastmiddelen:

- De plaats, datum en tijd van de contrast toediening - in het verslag van de beeldvorming en in het elektronisch patiëntendossier.
- De naam en dosis (volume, concentratie) van het specifieke contrastmiddel - in het verslag van de beeldvorming en in het elektronisch patiëntendossier.
- Het type overgevoeligheidsreactie, acuut of laat - in het verslag van de beeldvorming en in het elektronisch patiëntendossier.
- Alle symptomen en vitale parameters (bloeddruk, pols, ademsnelheid, zuurstof saturatie) van de patiënt - in het verslag van de beeldvorming en in het elektronisch patiëntendossier.
- De behandeling die werd gegeven en de respons van de patiënt daarop - in het verslag van de beeldvorming en in het elektronisch patiëntendossier.
- Gegevens van klinische follow-up en adviezen voor toekomsten premedicatie - in het verslag van de beeldvorming en in het elektronisch patiëntendossier.
- Gegevens over consultatie van een allergoloog over toekomstige contrastmiddeltoediening - in het elektronisch patiëntendossier.

Wanneer het om een ernstige of ongebruikelijke hypersensitiviteitsreactie gaat is de arts die verantwoordelijk is voor toediening van het contrastmiddel ook verantwoordelijk voor accurate rapportering naar de nationale farmacologie-autoriteit LAREB.

## Overwegingen

Primarily, in patients with a (documented) history of a hypersensitivity reaction to a contrast medium, an alternative imaging modality should be considered. The more severe the reaction, the stronger omitting a contrast medium should be considered. For mild reactions in which alternative imaging modalities are of substantially inferior quality, the risk – benefit ratio may shift. In many cases, CT with iodine-based contrast media can be replaced by ultrasound, with or without contrast agents, or MRI, with or without contrast agents. When this is not possible, consider performing the examination without a contrast medium, but only if this has an acceptable degree of diagnostic quality. For this, close communication with the referring specialist is mandatory.

*Use of premedication*
In premedication, two types of drugs are used: H1-antihistamines and corticosteroids. Often, they are used concomitantly, making their individual effect difficult to assess, particularly since there are many variations in premedication schedules. H1-antihistamine monotherapy is not common practice in Europe and the US, but has been used successfully in milder HSRs, particularly by Korean research groups.

H1-antihistamines block histamine receptors on various effector cells, blocking the effect of one of the pivotal players in direct mast cell responses. However, mast cells and basophils secrete various other substances that are not blocked by these drugs. The main side effect of the older H1-antihistamines that are available for intravenous administration is drowsiness/sedation. For the newer nonsedating antihistamines this effect is usually mild, but these are mainly available for oral administration.

Corticosteroids have various effect on the immune system, including mast cells, and therefore can block both mast cell degranulation by upregulating inhibitory signalling receptors, and inhibit cytokine production through suppression of gene transcription. (Andrade, 2004; Park, 2009) These membrane stabilizing effects require that administration is started >6h before contrast media administration. Unfortunately, this comes with a less favourable side effect profile, particularly with higher doses and repeated exposure.

The old protocols for premedication shown below (Greenberger, 1981; Greenberger, 1986; Lasser, 1994) are still in widespread use. The Greenberger protocol is popular in the USA, while the Lasser protocol is more frequently used in Europe. There is no literature to establish an optimal indication or protocol. Recently, the Greenberger protocol has been modified into shorter options with intravenous administration for inpatients (Mervak, 2017).

Greenberger protocol (elective examinations 1981, 1984):

- Prednisolone 50 mg IV - 13h, 7h and 1h before the procedure.
- Diphenhydramine 50 mg IV - 1h before the procedure.

Greenberger protocol (emergency examinations 1986):

- Hydrocortisone 200 mg IV - immediately and every 4h until procedure is finished.
- Diphenhydramine 50 mg IV - 1h before the procedure Lasser protocol (elective examinations 1994).
- Methylprednisolone 32 mg IV - 12h and 2h before the procedure.

The evidence regarding the effectivity of corticosteroids and antihistamines for pharmacological prevention is very heterogeneous and of low quality; moreover, it stems from the time of use of high osmolar, ionic ICM (Delaney 2006; Tramer, 2006; Davenport, 2017). It seems that prophylactic premedication can prevent the number of hypersensitivity reactions after contrast administration, but premedication mainly reduces the number of mild reactions and therefore the total number of reactions (Lasser, 1994), and not the number of severe reactions (Jung, 2016). It has been shown that premedication can cause brief hyperglycaemia (Davenport, 2010), but may also be associated with longer hospital stay, increased costs, and worse clinical outcomes (Davenport, 2016).

Few studies have focused on H1-antihistamine monotherapy, and these are biased to patients with mild reactions (Lee, 2016; Park, 2018). In a large Korean multicentre study logistic regression analysis showed that changing the ICM (odds ratio 0.51; 95% CI: 0.36, 0.73) and premedication with H1-antihistamines (odds ratio 0.53; 95% CI: 0.33, 0.86) were protective against recurrent reactions (Cha, 2019).

Many studies report a use of antihistamine and corticosteroid combination premedication; often these regimens are stratified according to the severity of the previous HSR (antihistamines only in mild HSR; antihistamines + corticosteroids in moderate to severe HSR) (Lee, 2016; Park 2017; Park, 2018) or adapted based to the clinicals preference. Corticosteroid monotherapy has rarely been used in older studies (from the high osmolar, ionic ICM era) and their findings cannot reasonably be extrapolated to the current low osmolar, nonionic contrast media (Lasser, 1994) To our knowledge, there are no studies available in which prescription of premedication has been randomized. The currently discussed studies show no additional beneficial effect of corticosteroid premedication in preventing a recurrent HSR. (Park, 2018; Cha, 2019)

Not surprisingly, the Joint Task Force on Practice Parameters of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology concluded in 2020 that “Evidence is lacking to support the role of glucocorticoid routine premedication in patients receiving low-osmolar or iso-osmolar ICMs to prevent recurrent radiocontrast media anaphylaxis” (Shaker, 2020).

In a recent study by McDonald (2021), published after our literature search, 1,973 high-risk patients with a history of HSR were retrospectively studied. Prophylactic measures consisted of changing the ICM and/or steroid premedication, with or without antihistamines. Only patients with a complete steroid premedication protocol (i.e., 2 doses of 32mg of methylprednisolone at 12 and 2 hours before) CT were include in the steroid group; patients with an incomplete protocol were put in the ‘not-steroid-premedicated’ group. In 4,360 examinations, 280 HSR occurred in 224 patients (11%), of which 19 (7%) were more severe than the previous HSR. Patients who received a different ICM with or without steroid premedication had a significantly lower rate of recurrent HSR than those who received the same ICM with steroid premedication (same ICM

and steroid premedication: 80 of 423 examinations [19%]; different ICM and no steroid premedication: 10 of 322 examinations [3%]; odds ratio [OR], 0.14 [95% CI: 0.06, 0.33]; P , .001; different ICM and steroid premedication: five of 166 patients [3%]; OR, 0.12 [95% CI: 0.04, 0.36]; P < .001). A sub analysis of the first CT scans only revealed that patients who received the same ICM had a similar risk of recurrent HSR, regardless of whether they received steroid premedication. (Steroid premedication: 44 of 172 patients [26%] vs. no premedication: 73 of 298 patients [25%]; OR, 1.00 [95% CI: 0.64, 1.57]; P = .99).

Although there is less data on the effectivity of premedication in GBCA, the few studies available show comparable results. Premedication with antihistamines and corticosteroid did not eliminate moderate or severe reactions to gadobenate dimeglumine (Bhatti, 2018). Both premedication protocols employed by Ryoo (2019) (antihistamine, systemic steroid plus antihistamine) did not show a recurrence-lowering effect, compared with the non- premedicated cases (antihistamine administration [OR, 1.180; 95% CI, 0.647–2.154; P = 0.589] and systemic steroid plus antihistamine [OR, 1.668; 95% CI, 0.609–4.565; P = 0.316]).

Finally, there is a paucity of data on the benefits of premedication for non-severe nonimmediate hypersensitivity reactions. Most of these reactions are self-limiting or can be treated symptomatically. In the very recent large Korean analysis, changing the type of GBCA and premedication were preventive, but premedication was only preventive in nonimmediate reactions (Ahn YH, 2022). Major international guidelines suggest performing allergologic skin testing, but do not recommend the use of premedication for non-severe nonimmediate reactions (ACR, 2022; ESUR, 2018; Torres, 2021).

Changing of a specific contrast medium

In recent years, changing the culprit ICM has become a frequently employed prophylactic strategy that is used as an alternative or a complementary measure to premedication, the latter particularly if the change has been made empirically without performing skin tests.

A large comparative study with 771 patients showed that changing the CM was more effective than premedication in the prevention of adverse reactions (Abe, 2016). Similar results were achieved in patient cohorts with mild or moderate-severe HSR where changing the contrast medium led to fewer recurrent HSR (Park, 2017; Park, 2018).

A large retrospective study on 1,963 patients showed that changing the culprit ICM only led to significantly lower rates of recurrent HSR, odds ratio of 0.14 [95% CI: 0.06, 0.33]. Additional, corticosteroid premedication did not offer additional protection, odds ratio of 0.12 [95% CI: 0.04, 0.36] (McDonald, 2021). In severe HSR, skin testing is useful to provide a safe alternative ICM (Ahn, 2022; Sohn, 2021).

In a very recent meta-analysis (Umakoshi, 2022), published after our literature search, six retrospective observational studies at moderate to severe risk of bias assessed 4,329 patients in the ICM-change-group and 2,826 in the no-change group. Changing ICM was associated with a reduced risk of recurrent hypersensitivity reaction by 61% (risk ratio = 0.39; 95% credible interval [CrI]: 0.24, 0.58). Adverse events associated with ICM-

change were not reported. It was concluded that in observational evidence of limited quality, ICM– change was associated with a reduced risk of recurrent immediate hypersensitivity reaction in patients with a prior ICM-induced hypersensitivity reaction.

In MRI, the experience of changing the culprit GBCA is more limited. In patients with mild immediate HSR, changing the contrast agent could reduce the recurrence rate (Ryoo, 2019). In a small study with mild to moderate HSR to a variety of linear and macrocyclic GBCA, empiric switching to gadoterate reduced the rate of recurrent HSR, independent of premedication with either corticosteroids and H1-antihistamines or corticosteroids only (Walker, 2021).

These findings are in line with the pathogenetic concept that the allergic reactions are not directed against a ubiquitous part of all ICM or GBCA (i.e., not against iodide), but are directed against a specific allergen that is unique to one or more contrast media; switching to a contrast medium that does not contain this epitope will prevent a recurrent allergic reaction. Unfortunately, the exact allergens/epitopes have not been identified and since contrast media are structurally related, the allergen may be present in other contrast media as well, leading to cross-reactivity for those specific agents. As a result, empiric switching of contrast media does not fully prevent a recurrent HSR. For ICM, the presence of the N-(2,3 dihydroxypropyl)-carbamoyl side chain may play a role in the HSR; after a HSR to an ICM containing this side chain, it is advised to switch to an ICM lacking this side chain (iobitridol, iopamidol), preferably supported by a negative skin test (Lerondeau, 2016).

*Evidence to decision*

There is no evidence that premedication reduces the risk of life-threatening anaphylactic reactions. The evidence for its role in less severe (moderate to mild) HSR remains weak and conflicting. Therefore, the GDG has decided to not advice premedication in patients with an history of immediate HSR to CM.

Corticosteroids do not appear to prevent immediate HSR to GBCA. Contrary, corticosteroids have significant side effects, particularly with cumulative use and in susceptible patients.

Antihistamines reduce the recurrence risk in milder reactions, but it remains uncertain if they also reduce the risk or ameliorate symptoms in moderate to severe reactions, as they are usually given in combination with steroids. Also, antihistamines have side effects, especially sedating side effects can occur (e.g., preventing driving a car). Changing the culprit CM as sole or complementary prophylactic measure significantly lowered the HSR recurrence rate for both ICM and GBCA.

Preferably the CM change is based on negative skin tests; if these are not available, an empiric but educated change should be performed, in which the currently known risks for cross-reactivity are considered (Table 1. Cross-reactivity rates between pairs of ICM in skin positive patients with immediate hypersensitivity reactions to iodine-based contrast media and Table 2. Cross-reactivity rates between pairs of ICM in skin positive patients with immediate hypersensitivity reactions to iodine-based contrast media). In case of an unknown previous culprit CM a testing dose of 10% of the alternative CM can be considered, especially in case of a previous severe reaction.

Breakthrough hypersensitivity reactions to contrast media

It's becoming increasingly clear that premedication is far from perfect. In premedicated patients so-called "breakthrough" hypersensitivity reactions can occur despite premedication. These are usually of similar severity as the original culprit reaction and are seldom severe (Davenport, 2017; Mervak 2015), but occasionally are of greater severity than the index reaction (Bhatti, 2018).

*Iodine-based contrast media*

A large study of antihistamine premedication in patients with mild HSR showed no benefit of premedication with a breakthrough reaction frequency of 11%, identical to using no premedication (Lee, 2016).

In a study using a stratified premedication protocol, the frequency of breakthrough reactions was 17%. Most of these reactions (89%) were mild and required no treatment. In severe HSR underdosage of premedication led to a significant increase in breakthrough reactions (Lee, 2017).

Kim (2018) studied the effect of the administration route on breakthrough reactions. Re- exposure to intravascular CM yielded a breakthrough frequency of 19,5%. The number of reactions after extravascular CM was negligible.

*Gadolinium-based contrast agents*

Walker (2019) showed a high rate (35%) of breakthrough reactions in patients with HSR to gadobutrol. Both culprit and breakthrough HSR were usually mild but may escalate in severity. This rate is very similar to the rate in a previous large prospective study on HSR after gadobutrol (Power, 2016).

In a meta-analysis of breakthrough reactions, a similar 39% rate of breakthrough HSR was found. The frequency was similar between macrocyclic and protein-binding linear GBCA (Walker, 2020).

*Evidence to decision*

The frequency of breakthrough reactions varies on the severity of the culprit reaction and the specific premedication protocol. Rates after ICM vary between 2-20%, but rates after GBCA administration are higher, in the order of 35-40%. Most of the reactions are of similar severity as the culprit reaction, but incidental escalation in severity may be found.

Cross-reactivity between specific contrast media (see also Introduction to chapter 3.5 Follow up strategieën na hypersensitiviteitsreacties na CM)

In most studies on contrast media hypersensitivity, the term cross-reactivity is used when patients have a HSR to two or more different contrast media, or if there are positive skin tests for two or more contrast media. In the latter case, it is not always entirely certain whether the skin test positivity is clinically relevant, as a drug provocation test is generally not performed. It has recently been suggested to discriminate polyvalent

reactivity from cross-reactivity. Polyvalent reactivity comprises patients that have positive skin tests to multiple contrast media. It is argued that the term cross-reactivity should be reserved for polyvalent reactivity within a defined chemical group (e.g., with a N-(2,3 dihydroxypropyl)- carbamoyl side chain), and that multiple positive reactions against non-group CM should be defined as individual reactivity that is probably more prominent between contrast media (Schmid, 2021). However, this is a much stricter definition than has been used in most studies and for clarity we here stick to the broader definition of cross-reactivity.

*Iodine -based contrast media*

Schrijvers (2018) found most cross-reactivity between agents with a N-(2,3 dihydroxypropyl)-carbamoyl side chain. For immediate HSR, iomeprol and iopromide showed the highest test positivity (41%), while for nonimmediate HSR this was between ioversol and iomeprol (55%) (Table 1. Cross-reactivity rates between pairs of ICM in skin positive patients with immediate hypersensitivity reactions to iodine-based contrast media and Table 2. Cross-reactivity rates between pairs of ICM in skin positive patients with immediate hypersensitivity reactions to iodine-based contrast media).

Sohn (2021) showed in 250 patients with positive skin tests, polyvalent reactivity to at least 2 different ICM in 157 patients. The highest frequency was between iomeprol and iohexol (36%). The frequency was higher in pairs with common N-(2,3 dihydroxypropyl)-carbamoyl side chains than between CM with non-common side chains. This was significant for severe immediate HSR. In contrast, Gamboa (2021) found in IgE-mediated allergic reactions that cross-reactivity of iomeprol with iopamidol, iopromide, and iobitridol was low. In their study, iopamidol was a valid alternative in patients with IgE-mediated allergy to iomeprol and negative skin tests to iopamidol. The culprit ICM itself can be administered safely in patients having experienced nonallergic immediate hypersensitivity. In the CIRTACI study on immediate HSR it was also shown that cross-reactivity was predominantly present in allergic immediate reactions, but seldom in nonallergic immediate HSR (Clement, 2018).

In 43 patients with skin tests for nonimmediate HSR, Gaudin (2019) showed a high rate of cross-reactivity between ICM, that followed the Lerondeau classification (Lerondeau, 2016). Iobitridol was a well-tolerated alternative ICM in 77% of patients. Very similar findings have been found in a 19/142 patients with non-immediate HSR and positive intradermal tests (Gracia Bara, 2019).

In an older meta-analysis of 21 studies on skin testing, extensive data are presented on the frequency of cross-reactivity in immediate and nonimmediate reactions (Yoon, 2015). The percentage of cross-reactivity is in general lower than the percentages found in other studies (Schrijvers, 2018: Sohn, 2021). This may be related to the inclusion of older studies with a lower overall positive yield of the skin test.

**Table 1. Cross-reactivity rates between pairs of ICM in skin positive patients with non-immediate hypersensitivity reactions to iodine-based contrast media**

| ICM Name | Iobitridol | Iopamidol | Iopromide | Iohexol | Iomeprol | Ioversol | Iodixanol |
|---|---|---|---|---|---|---|---|
| Iobitridol | X | | | | | | |
| Iopamidol | **11.8%** [5.5-18] | X | | | | | |
| Iopromide | **22.1%** [22-22.2] | **25.6%** [11.1-40] | X | | | | |
| Iohexol | **20.8%** [16.6-25] | **25.1%** [11.1-39] | **43.5%** [38.9-48] | X | | | |
| Iomeprol | **17.6%** [13-22.2] | **33.2%** [33-33.3] | **38.7%** [33-44.4] | **40.2%** [36-44.4] | X | | |
| Ioversol | **20.6%** [19-22.2] | **35.6%** [22.2-49] | **37.7%** [33.3-42] | **50.0%** [38.9-61] | **53.3%** [51-55.5] | X | |
| Iodixanol | **19.3%** [16.6-22] | **36.6%** [22.2-51] | **45.5%** [38.9-52] | **51.7%** [44.4-59] | **45.5%** [41-50] | **51.5%** [38.9-64] | X |

Average percentages and [range] of findings by Yoon 2015, Schrijvers 2018 and Sohn 2021. ICM containing the common *N*-(2,3-dihydroxypropyl) carbamoyl side chain is grouped within the black line. Risk of cross-reactivity is marked as very low (dark green, <10%), low (green, 10-20%), medium (orange 20-30%), high (red, 30-50%) and very high (dark red, >50%).

## Table 2. Cross-reactivity rates between pairs of ICM in skin positive patients with immediate hypersensitivity reactions to iodine-based contrast media

| ICM Name | Iobitridol | Iopamidol | Iopromide | Iohexol | Iomeprol | Ioversol | Iodixanol |
|---|---|---|---|---|---|---|---|
| Iobitridol | X | | | | | | |
| Iopamidol | **12.7%** [5.9-22.1] | X | | | | | |
| Iopromide | **10%** [5.9-12.1] | **14.3%** [11.7-19.1] | X | | | | |
| Iohexol | **9.8%** [5.9-16.4] | **11%** [8-14] | **12.8%** [5.9-23.6] | X | | | |
| Iomeprol | **10.8%** [5.9-16.6] | **10%** [6-14] | **27.9%** [21-41.1] | **22.2%** [1-36.3] | X | | |
| Ioversol | **8.4%** [6-10.8) | **8%** [5-10.9] | **12.2%** [4-20.4] | **15.3%** [7-23.5] | **19.7%** [8-29.4] | X | |
| Iodixanol | **9.9%** [7-12.8] | **6.3%** [5-7.6] | **12.4%** [9-16.6] | **16%** [10-20.4] | **15.5%** [11-17.8] | **14.3%** [5-20.4] | X |

Average percentages [range] of findings by Yoon, 2015 and Schrijvers, 2018. ICM containing the common *N*-(2,3- dihydroxypropyl) carbamoyl side chain are grouped within the black lines. Risk of cross-reactivity is marked as very low (dark green, <10%), low (green, 10-20%), medium (orange 20-30%), high (red, 30-50%) and very high (dark red, >50%).

*Gadolinium-based contrast agents*

The CIRTACI study showed that a high percentage of Ring-Mesmer type 3-4 reactions after contrast media administration were allergic. Cross-reactivity among GBCA was only shown in these allergic immediate HSR. The overall number of cross-reactivity reactions was higher for GBCA than for ICM, but the number of patients was low for GBCA (Clement, 2018).

In a 7-year retrospective analysis of patients with hypersensitivity to GBCA, 13,6% (18/132) had positive skin tests and were deemed allergic. Cross-reactivity occurred in 38% and was more frequent among the macrocyclic GBCA. Cross-reactivity between macrocyclic and linear GBCA also occurred (Mankouri, 2021).

In a small retrospective study, Grüber (2021) showed cross-reactivity among macrocyclic GBCA and between macrocyclic and linear GBCA, but not among linear GBCA.

In a small case-series of 5 patients with immediate HSR to gadobutrol, only cross-reactivity with gadoterate was demonstrated (Gallardo-Higueras, 2021).

*Evidence to decision*

In ICM cross-reactivity is common in allergic immediate and even more in nonimmediate HSR. It occurs most frequently among ICM with a common N-(2,3 dihydroxypropyl)- carbamoyl side chain such as iopromide, iohexol, ioversol, iomeprol and iodixanol.

In GBCA cross-reactivity in allergic HSR is more common than with ICM and is especially prevalent among macrocyclic GBCA.

Serum tryptase evaluation and skin testing are key in diagnosing allergic vs. nonallergic HSR and skin tests can identify safe alternative contrast media for future diagnostic studies.

Unknown severity of previous hypersensitivity reaction to contrast media

Unfortunately, there is a lack of data about the recurrence rate and severity of HSR to CM of patients in which there is no data about the severity of the initial HSR. Although in our daily practice this is a substantial part of the population, in studies these patients are not included. Therefore, we want to stress the importance of proper documentation (see below).

A practical guideline to assess the severity of the initial reaction can be adapted from the Hartwig's Severity Assessment Scale (Hartwig, 1992):

- Did the hypersensitivity reaction to contrast media caused permanent harm to the patient?
- Was the hypersensitivity reaction to contrast media reason for admission to the hospital or reason for increasing of hospital stay?
- Was the hypersensitivity reaction to contrast media treated with an adrenaline auto- injector (Epipen)?

The GDG advice to treat patients in line with a previous mild reaction if these questions are answered with 'no'. In case one of these questions is answered with 'yes' patient should be treated as having a previous severe reaction.

Documentation of hypersensitivity reactions to contrast media

With an increasing use of changing between specific contrast media and the use of skin testing for identifying possible safe alternatives to culprit contrast media causing hypersensitivity reactions, proper documentation in the electronic patient record (EPR) has become very important.

However, the practice is quite different. Documentation in the EPR is not well standardized, is often done by physicians without any experience in the administration of contrast media, and is therefore often insufficient and incomplete (Ananthakrishnan, 2021; Deng, 2019). Recommendations for standardization have recently been published (Böhm, 2020). In selected institutions semi-structured tools for documentation of adverse events have only just been developed and implemented (Lang, 2022).

We would like to re-iterate the recommendations from Safe Use of Contrast Media, part 2: It is mandatory

that the *physician responsible for the administration of the CM or (EPR only) the drug allergy specialist* accurately records the following:

- The place, date, and time of CM administration in the imaging report and in the electronic patient record.
- The specific contrast medium name and dose (volume, concentration) in the imaging report and in the electronic patient record.
- The type of hypersensitivity reaction, immediate or non-immediate, in the imaging report and in the electronic patient record.
- All patient symptoms and vital signs (blood pressure, pulse, respiration rate, oxygen saturation) in the imaging report and in the electronic patient record.
- The treatment given, and the response of the patient to the treatment in the imaging report and in the electronic patient record.
- Any clinical follow-up and advice on need for future premedication in the imaging report and in the electronic patient record.
- Any results of the consultation with a drug allergy specialist on future CM administration in the electronic patient record.

In addition:

- The presence of a documented allergic or nonallergic hypersensitivity reaction in the electronic patient record allergy registry ("allergie registratie"). It is essential that this reporting should be based on the name of the specific contrast medium and be done by *radiologists/cardiologists or drug allergy specialists* with experience in the use of contrast media.
- If the adverse reaction to a contrast medium is severe or unusual, the *physician responsible for the administration of the CM or the drug allergy specialist* should report all details of the reaction to the National Pharmacovigilance Authority (LAREB).

**Recommendations and flowcharts**

| |
|---|
| In all patients with a (documented) history of a hypersensitivity reaction to an iodine-based contrast medium or a gadolinium-based contrast agent, consider an alternative imaging modality. When this is not possible, consider performing an unenhanced exam, but only if the reduction in diagnostic quality is acceptable.<br><br>*See also flow charts |

1. Patients with previous immediate (acute) hypersensitivity reactions to iodine-based contrast media or gadolinium-based contrast agents

In patients with a (documented) history of a **mild immediate** hypersensitivity reaction to an iodine-based contrast medium or a gadolinium-based contrast agent:

- Treat these patients as any other patient because of the low risk of developing a moderate or severe reaction

*See also flow charts

In patients with a (documented) history of a **moderate or severe** hypersensitivity reaction to iodine-based contrast media or gadolinium-based contrast agents

- Postpone imaging and refer the patient to a drug allergy specialist

If there is no time to refer the patient to a drug allergy specialist:

- Choose a different iodine-based contrast medium or gadolinium-based contrast agent, if the culprit contrast medium is known*
- Consider a test dose by first giving 10% of the total contrast dose and observing the patient for >15 minutes; particularly with severe reactions and/or unknown culprit
- Observe the patient ≥ 30 min with IV in place
- Be vigilant to react to a possible new hypersensitivity reaction

*See also flow charts

2. Patients with a previous breakthrough reaction to contrast media

In patients with a breakthrough hypersensitivity reaction to iodine-based contrast media or gadolinium-based contrast agents, always refer to a drug allergy specialist for skin testing with a panel of different iodine-based contrast media or gadolinium-based contrast agents.

*See also flow charts

3. Patients with previous hypersensitivity reactions to multiple contrast media

In patients with hypersensitivity reactions to multiple iodine-based or gadolinium-based contrast media (either two or more different iodine-based contrast media or gadolinium- based contrast agents or to an iodine-based contrast medium and a gadolinium-based contrast agent) apply the same as above, but always refer the patient to a drug allergy specialist.

*See also flow charts

4. Patients with previous nonimmediate (delayed) hypersensitivity reactions to iodine-based contrast media or gadolinium-based contrast agents

- Do **not** give iodine-based contrast media or gadolinium-based contrast agents to a patient with a previous (suspected) severe nonimmediate skin eruption with danger signs[1]
- Refer the patient immediately to a drug allergy specialist

In patients with a history of a mild-moderate nonimmediate skin eruption without danger signs[1]:

- Choose a different iodine-based contrast medium or gadolinium-based contrast agent if the culprit contrast medium is known[2]
- Instruct the patient in case of a recurrent reaction to take pictures of the skin lesions and contact the radiology or cardiology department for feedback

*See also flow charts

[1] Danger signs: erosive and/or haemorrhagic lesions, blistering and skin disruption, mucosal involvement, extracutaneous organ involvement (high fever, abnormal liver / kidney values, lymphadenopathy)
[2] Consider cross-reactivity of contrast media (see Table 1. Cross-reactivity rates between pairs of ICM in skin positive patients with immediate hypersensitivity reactions to iodine-based contrast media and Table 2. Cross-reactivity rates between pairs of ICM in skin positive patients with immediate hypersensitivity reactions to iodine-based contrast media) and an increased risk for NIHR with use of iso-osmolar ICM.

Assessment of severity of previous hypersensitivity reaction when information in patient file is lacking can be performed by asking patient the following questions:

- Did the hypersensitivity reaction to contrast media caused permanent harm to the patient?
- Was the hypersensitivity reaction to contrast media reason for admission to the hospital or reason for increasing of hospital stay?
- Was the hypersensitivity reaction to contrast media treated with an adrenaline auto- injector (Epipen)?

The GDG advice to treat patients in line with a previous mild reaction if these questions are answered with ‘no’. In case one of these questions is answered with ‘yes’ patient should be treated as having a previous severe reaction.

*See also flow charts

## 5. Cross-reactivity between contrast media

Cross-reactivity is most relevant in *allergic* hypersensitivity reactions. It occurs with a higher frequency among:

- Iodine-based contrast media with a *N*-(2,3 hydroxypropyl)-carbamoyl side chain
- Macrocyclic gadolinium-based contrast agents

The drug allergy specialist determines through skin testing with a panel of different iodine-based contrast media and gadolinium-based contrast agents:

- The allergic nature of the hypersensitivity reaction
- Cross-reactivity between contrast media
- Suggestions of safe alternative contrast media

6. Documentation of hypersensitivity reactions

The physician responsible for the administration of the contrast medium should accurately document the hypersensitivity reaction in the imaging report.

The physician responsible for the administration of the contrast medium or the drug allergy specialist should accurately document the hypersensitivity reaction in the electronic patient dossier.

It is essential that reporting should be based on the name of the *specific* contrast medium and be done by *physicians or drug allergy specialists* with experience in the use of contrast media.

After all hypersensitivity reactions to contrast media, the following should be registered:

- The place, date, and time of CM administration - in the imaging report and in the electronic patient record.
- The specific contrast medium name and dose (volume, concentration) - in the imaging report and in the electronic patient record.
- The type of hypersensitivity reaction, immediate or non-immediate - in the imaging report and in the electronic patient record.
- All patient symptoms and vital signs (blood pressure, pulse, respiration rate, oxygen saturation) - in the imaging report and in the electronic patient record.
- The treatment given, and the response of the patient to the treatment - in the imaging report and in the electronic patient record.
- Any clinical follow-up and advice on need for future premedication - in the imaging report and in the electronic patient record.
- Any results of the consultation with a drug allergy specialist on future CM administration - in the electronic patient record.

The physician responsible for the administration of the contrast medium or the drug allergy specialist should accurately document severe or unusual hypersensitivity reactions to the National Pharmacovigilance Authority LAREB.

*See also Introduction to chapter 3.5 Follow up strategieën na hypersensitiviteitsreacties na CM

## Onderbouwing

## Onderbouwing

### Achtergrond

Patients reporting a previous hypersensitivity reaction (HSR) to contrast media are at increased risk of developing a recurrent hypersensitivity reaction upon re-exposure (see Module 3.5.3 Risk Factors for Hypersensitivity Reactions to Contrast Media). It is unclear what the best strategy is to prevent such a recurrent hypersensitivity reaction.

Options include complete avoidance of contrast media and performing alternative imaging techniques, which may lead to inferior quality of the diagnostic modality or higher costs, depending on the modality used. Alternatively, contrast media can be alternated to a different agent, and/or so-called premedication may be employed. Premedication consists of antihistamines with or without corticosteroids, with the aim to prevent a hypersensitivity reaction. Different protocols for premedication (Greenberger, 1981; Greenberger, 1984; Greenberger, 1986; Lasser, 1994) are still in widespread use, often slightly modified, but there is no literature to establish an optimal indication or protocol. The older protocols have been challenged by newer, shorter options for inpatients (Mervak, 2017). Moreover, the use of premedication is a current topic of debate, as the literature on the effectiveness of premedication prior to CM administration remains unclear and particularly corticosteroids have relevant adverse effects.

All types of contrast media can give hypersensitivity reactions. See chapter 3.5 Follow-up Strategies after Hypersensitivity Reactions to Contrast Media.

All types of contrast media will be evaluated: iodine-based, gadolinium-based, microbubble, CM. Also, all types of administration routes will be covered, intravascular (intravenous or intra-arterial), oral and rectal, intracavitary (joints or bladder), and intraductal (bile or pancreatic ducts). See separate chapter for nonvascular CM administration.

### Conclusies / Summary of Findings

| | |
|---|---|
| **Very low GRADE** | The evidence is very uncertain about the effect of premedication on hypersensitivity reactions to contrast media when compared with no premedication or a different premedication strategy in patients undergoing examinations with iodine-based contrast media.<br><br>*Cha, 2019; Mervak, 2017; Park, 2017; Park, 2018; Specjalski, 2020; Tramer, 2006* |

| | |
|---|---|
| **Very low GRADE** | The evidence is very uncertain about the effect of premedication on hypersensitivity reactions to contrast when compared with no premedication or a different premedication strategy in patients undergoing examinations with gadolinium-based contrast agents.<br><br>*Bhatti, 2018; Ryoo, 2019; Walker, 2021* |

## Samenvatting literatuur

Description of studies – Iodine-based contrast media

Cha (2019) described a multicentre registry study aiming to identify the prevalence, patterns, risk factors, and preventive measures for ICM-related HSRs. Between March 2017 and October 2017, a total of 196 081 patients who underwent contrast-enhanced CT examinations using ICM were enrolled from seven participating institutions. Regimens for premedication were as follows: for patients who reported a mild index reaction, 4 mg of intravenous chlorpheniramine 30 minutes before ICM administration; for patients who reported a moderate index reaction, 40 mg of intravenous methylprednisolone and 4 mg of intravenous chlorpheniramine 1 hour before ICM administration; and for patients who reported a severe index reaction, 40 mg of intravenous methylprednisolone 4 hours and 1 hour before ICM administration and 4 mg of intravenous chlorpheniramine 1 hour before ICM administration via the intravenous cannula inserted for ICM injection.

Mervak (2017) described a retrospective cohort study aiming to determine if the allergic-like breakthrough reaction rate of intravenous corticosteroid prophylaxis administered 5 hours before contrast material–enhanced CT is noninferior to that of a traditional 13-hour oral regimen. All subjects were premedicated for a prior allergic like or unknown-type reaction to iodine-based contrast material. A noninferiority margin of 4.0% was selected to allow for no more than a clinically negligible 6.0% breakthrough reaction rate in the cohort that received 5-hour intravenous corticosteroid prophylaxis. The breakthrough reaction rate for a cohort of 202 patients who received accelerated 5-hour IV corticosteroid prophylaxis before contrast material–enhanced CT for a prior allergic-like or unknown-type reaction to iodine- based contrast media was compared with a previously published breakthrough reaction rate from the same institution for a similar group of subjects who received a 13-hour oral premedication regimen for the same indication (2.1%; 13 of 626). Only allergic-like breakthrough reactions were considered for this study; physiologic reactions were ignored, because they are not considered relevant to corticosteroid prophylaxis.

Park (2017) described a retrospective cohort study aiming to evaluate the outcomes of re- exposure to low osmolar iodine-based contrast medium (LOCM) in patients with a history of moderate-to-severe hypersensitivity reaction (HSR) who underwent contrast-enhanced computed tomography after the initial HSR. Premedication was defined as antihistamines or systemic steroids prescribed with the aim of preventing recurrence of HSR. The premedication regimens used at the time of re-exposure were determined according to the decision of the physicians in charge. Steroids and antihistamines were administered 0.5–1 hour before re-exposure to LOCM.

Park (2018) described a retrospective cohort aiming to evaluate premedication protocols involving administration of antihistamines and multidose corticosteroids that have
been widely used in prevention of recurrent HSRs to ICM. The outcomes of patients with mild HSR who

subsequently underwent contrast material–enhanced CT between January 2012 and December 2015 were analysed. For premedication, 4 mg of chlorpheniramine was intravenously administered 30 minutes prior to re-exposure to ICM For patients with a mild index reaction. The initial HSR event was defined as the first occurrence of an immediate HSR to ICM. Recurrent HSR events were defined as an immediate HSR at repeated exposure to ICM after the initial event.

Specjalski (2020) described a prospective observational study aiming to determine efficacy of premedication before medical procedures with the use of iodine-based contrast media in patients with a history suggesting a hypersensitivity reaction after their past use. Out of 152 patients consulted due to adverse reactions after ICM (85 women and 67 men, aged 43–90), 101 were selected with a history suggesting a mild hypersensitivity reaction (urticaria, itching, skin redness, malaise etc.). All patients had an indication for ICM administration in the near future. Premedication was given with cetirizine (10 mg) and prednisone (20 mg or 50 mg, randomly assigned) 13, 7 and 1 h before the ICM administration. Patients with a history of a severe drug hypersensitivity reaction, including anaphylaxis, unstable asthma, renal insufficiency, or unstable heart insufficiency were excluded from the study. They also excluded patients with isolated subjective vasomotor symptoms (nausea, sweating, feeling of warmth etc.). Patients were randomly assigned to one of the premedication arms: 10 mg cetirizine + 20 mg prednisone or 10 mg cetirizine + 50 mg prednisone. The premedication was given orally 13, 7 and 1 h before the ICM administration. Subjects were observed 24 h after the ICM administration.

One systematic review (Tramer, 2006) included 9 RCTs in this analysis. The goal of this review was to review the efficacy of pharmacological prevention of serious reactions to iodine-based contrast media. A systematic search was performed up to October 2005. The pre-specified inclusion criteria were random allocation of patients, use of premedication alone or in combination, presence of a placebo or a no treatment control group, and reporting of presence or absence of allergic reactions. A total of 9 trials with 10,011 adult patients were included in the review analysis. No RCTs that answered the search questions were found that were published after this systematic review.

Description of studies – Gadolinium-based contrast agents

Bhatti (2018) described a retrospective cohort study aiming to determine the severity of breakthrough reactions to gadobenate dimeglumine in patients premedicated with a 13- hour premedication regimen. The final study population consisted of 19 breakthrough reactions to gadobenate dimeglumine in 19 subjects (18 female, 1 male) with a mean age of 51 years (range, 28-90 years) and a mean administered volume of gadobenate dimeglumine of 17 mL (range, 9-30 mL). Hypersensitivity reactions to gadobenate that were not preceded by premedication (n = 97) were explored as a comparator group. All premedication regimens were 13 hours in length, consisting of 150 mg oral prednisone (50mg 13, 7, and 1 hour before contrast material) and 50 mg oral diphenhydramine (1 hour before contrast material).

Ryoo (2019) described a retrospective cohort study aiming to evaluate the effectiveness of changing the contrast agent and single-dose premedication for HSR recurrence prevention in patients with a history of mild immediate HSR to GBCA who subsequently underwent enhanced magnetic resonance imaging. Intravenous chlorpheniramine 4 mg, 30 minutes before the GBCA administration, or intravenous methylprednisolone sodium succinate 40 mg plus chlorpheniramine 4 mg, 1 hour before the GBCA administration, was

administrated as premedication regimen. Recurrence rates of immediate HSR were compared according to prevention strategies. The GBCA that was used at the initial HSR event was defined as the culprit agent. An immediate HSR event at re-exposure to a GBCA after the initial HSR was defined as recurrent HSR.

Walker (2021) described a prospective observational efficacy trial aiming to evaluate HSR rate to GBCA among patients with history of HSR to GBCA, empirically given an alternative GBCA prior to repeat administration. Patients with prior HSR to GBCA received 13-hour oral corticosteroid and diphenhydramine premedication prescription with switching of GBCA to gadoterate.

Results – Iodine-based contrast media

Cha (2019) studied 196081 patients (mean age 59.1 ±16.0 years; 53% men) who underwent ICM administration. The overall prevalence of HSRs was 0.73% (1433 of 196081), and severe reactions occurred in 0.01% (17 of 196081). Among the 196081 patients, 570 patients reported experiencing an HSR to ICM in the past, and 94.9% (541 of 570) patients underwent preventive measures before ICM administration. Premedication only was conducted in 213 patients (37.4%, 213 of 570; 187 patients received antihistamine only and 26 patients received antihistamine with corticosteroids) and change of ICM only was performed in 52 patients (9.1%, 52 of 570). In 276 patients (48.4%, 276 of 570), both premedication and change of ICM were performed (203 received antihistamine with change of ICM and 73 received antihistamine and corticosteroids with change of ICM).

Among 570 patients who had experienced an HSR to ICM in the past, 195 patients experienced recurrent HSR, whereas 375 patients did not show any symptoms of recurrence. A total of 176 of 541 patients (32.5%) experienced recurrent HSR despite premedication and/or change of ICM. Of those 176 patients, 158 patients received pretreatment (n= 131 antihistamines only, n= 27 antihistamines plus corticosteroids) and their reactions were thus considered breakthrough reactions. In addition, recurrent events occurred in 92 of 328 (28.1%) patients for whom culprit agents were changed. Logistic regression analysis showed that use of premedication with antihistamine (OR, 0.5; P = .01) and change in the generic profile of ICM (OR, 0.5; P < 0.001) were preventive against recurrent HSR.

Mervak (2017) showed that significantly more subjects receiving a 13-hour oral regimen had a prior reaction to iodine-based contrast material of unknown type (38% vs 15%, P= .0001), and significantly more subjects who received an accelerated IV regimen had a prior mild reaction to iodine-based contrast material (51% vs 34%, P=.0001). The breakthrough reaction rate for 5-hour intravenous prophylaxis was 2.5% (five of 202 patients; 95% CI: 0.8%, 5.7%), which was noninferior to the 2.1% (13 of 626 patients; 95% CI: 1.1%, 3.5%) rate for the 13-hour regimen (P =.018). The upper limits of the confidence interval for the difference between the two rates was 3.7% (0.4%; 95% CI: 21.6%, 3.7%), which was within the 4.0% noninferiority margin. All breakthrough reactions were of equal or lesser severity to those of the index reactions (two severe, one moderate, and one mild reaction).

Park (2017) included 150 patients from the 11 included centres. The proportion of males was 49.3% and the mean age was 61.7 ± 11.5 years. Among a total of 328 cases of re- exposure, the ICM was changed in 59.1% and systemic steroids were administered as premedication in 37.2% of cases at the time of re-exposure.

Among 180 re-exposures without steroid premedication following moderate initial HSR, changing the ICM significantly reduced the recurrence rate of HSR (22.5% vs. 11.0%; P = 0.037). Among 92 re-exposures premedicated with systemic steroids following moderate initial HSR, the recurrence rate of HSR did not significantly differ (30.6% vs. 16.1% with the same vs. different ICM; P = 0.100). Among 23 re-exposures without steroid premedication following severe initial HSR, the recurrence rate was similar irrespective of whether the same ICM was used or not (33.3% vs. 23.5%; P = 0.632). On the other hand, among 26 cases premedicated with systemic steroids following a severe initial HSR, the recurrence rate was only 9.5% (2/21) when a different ICM was used, whereas four out of five cases (80.0%) using the same ICM experienced recurrence (P = 0.005). Steroid premedication did not result in improvement of the overall outcomes at the subsequent re-exposure (16.5% vs. 23.0%, P = 0.250). Next, the subjects premedicated with systemic steroids into two groups were divided according to the dose of steroids. The recurrence rate of HSR was not statistically different between subjects premedicated with a steroid equivalent to < 40 mg (19.7%; 13/66) or ≥40 mg of prednisolone (26.8%; 15/56) (P = 0.353) The risk of recurrent HSR was 67.1% lower in cases where the implicated ICM was changed to another one (OR: 0.329; P = 0.001). However, steroid premedication did not show protective effects against recurrent HSR.

Park (2018), report a total of 1178 patients (men 47.5%, 55.8 ±11.2 years) with mild immediate HSR were re-exposed to ICM 3533 times. Among these patients, 1056 patients (89.6%) experienced allergy-like reactions and 122 patients (10.4%) developed gastrointestinal reactions. Premedication with an antihistamine had a significant recurrence- lowering effect; the recurrence rate was 16.6% in non-premedicated patients, but decreased to 10.7% when antihistamine premedication was administered (OR, 0.569; 95% CI: 0.443, 0.731; P=.001) Regardless of whether contrast media was replaced or not, administration of antihistamine premedication lowered the recurrence rate significantly (with the same contrast media: OR, 0.627; 95% CI: 0.430, 0.912; P = .015; with different contrast media: OR, 0.584; 95% CI: 0.4240, 0.776; P=.001) With re-exposure to the culprit agent without premedication, the recurrence rate was 31.1% (85 of 273 examinations). The recurrence rate decreased to 12% (105 of 872 examinations; P=.001) by only changing the culprit agent and to 7.6% (148 of 1947 examinations; P=.001) by using the combination of changing the ICM and antihistamine premedication. Changing the ICM plus antihistamine premedication was also helpful in reducing the recurrence of gastrointestinal symptoms from 16.1% to 1.8% (P=.020). However, despite changing of the ICM, some combinations of ICM did not show a prophylactic effect.

In Specjalski (2020), 76 patients underwent the radiologic procedure with premedication with antihistamine and a lower (40 patients; 3x 20mg) or higher dose (36 patients; 3x 50mg) of prednisone. Four of them (5%) reported a cutaneous hypersensitivity reaction (urticaria, itching, redness) and one dyspnoea. There was no statistically significant difference in relation to the premedication protocol (p = 0.1306).

Tramer (2006) reported 9 trials (including 10,011 adults) tested H1 antihistamines, corticosteroids, and an H1 +H2 blocker combination. No trial included exclusively patients with a history of allergic reactions. Many outcomes were not allergy related, and only a few were potentially life threatening. No reports on death, cardiopulmonary resuscitation, irreversible neurological deficit, or prolonged hospital stays were found. In two trials, 3/778 (0.4%) patients who received oral methylprednisolone 2×32 mg or intravenous prednisolone 250 mg had laryngeal oedema compared with 11/769 (1.4%) controls (odds ratio 0.31, 95% confidence interval

0.11 to 0.88). In two trials, 7/3093 (0.2%) patients who received oral methylprednisolone 2×32 mg had a composite outcome (including shock, bronchospasm, and laryngospasm) compared with 20/2178 (0.9%) controls (odds ratio 0.28, 0.13 to 0.60). In one trial, 1/196 (0.5%) patient who received intravenous clemastine 0.03 mg/kg and cimetidine 2 to 5 mg/kg had angio-oedema compared with 8/194 (4.1%) controls (odds ratio 0.20, 0.05 to 0.76).

Results – Gadolinium-based contrast agents

Bhatti (2018) showed that premedication was most commonly given (63% [12/19]) for a previous hypersensitivity reaction to gadolinium-based contrast media (GBCM); in 37%(7/19), it was given for a different risk factor. In those premedicated for a previous allergic-like reaction to GBCM of known severity (n = 9), the breakthrough reaction severity was the same as index reaction severity in 56% (5/9), less severe in 11% (1/9), and of greater severity in 33% (3/9). Two severe breakthrough reactions occurred; both were in subjects premedicated for risk factors other than a previous GBCM reaction. No subjects died. Five subjects were re-exposed to GBCM a total of 9 times; no repeat breakthrough reactions occurred.

Ryoo (2019) studied a total of 185 patients with a history of mild immediate HSR to GBCA who were re-exposed to GBCA 397 times during the study period. The overall recurrence rate was 19.6% (78/397). Changing the culprit GBCA significantly reduced the recurrence rate, compared with reusing the culprit GBCA (6.9%, 9/130 and 25.8%, 69/267; P < 0.001). The recurrence rate was lowest when the GBCA was changed to a different molecular structure class from the culprit agent, followed by changing to CM with the same molecular structure and reusing the culprit GBCA (6.2%, 7/113 vs 11.8%, 2/17 vs 25.8%, 69/267; P < 0.001). Single-dose premedication demonstrated no significant prophylactic effect on recurrence (20.4%, 17/98 vs 17.3%, 61/299 with and without premedication, respectively; P= 0.509). The recurrence rate of cases with antihistamine administration was 19.9%, and the recurrence rate of cases with systemic steroid plus antihistamine administration was 25.9%. Both premedication protocols did not show a recurrence-lowering effect, compared with the non-premedicated cases (antihistamine administration [OR, 1.180; 95% CI, 0.647–2.154; P = 0.589] and systemic steroid plus antihistamine [OR, 1.668; 95% CI, 0.609–4.565; P = 0.316]). Premedication in addition to changing CM also showed no additional prophylactic effect (7.2%, 7/97 and 6.1%, 2/33, respectively; P = 0.821).

Walker (2021) evaluated 26 patients with mild (92.3% [24/26]) or moderate (7.7% [2/26]) HRS to gadobutrol (53.8% [14/26]), gadoxetate (3.8% [1/26]), and gadopentetate (3.8% [1/26]). In 38.5% (10/26), inciting GBCA was unknown but was likely gadobutrol or gadopentetate based on availability. Most patients were female (84.6% [22/26]). The mean patient age was 52.1 ± 15.8 years. From 27 gadoterate administrations, 59.3% (16/27) patients received corticosteroid and diphenhydramine premedication, 11.1% (3/27) received only diphenhydramine, and 29.6% (8/27) with no premedication. Among the 26 included patients, 2 patients, both female, with a history of immediate HR to gadobutrol had a breakthrough HR to gadobutrol despite adequately dosed corticosteroid premedication. Hypersensitivity reaction rate after empiric switching to gadoterate was 3.7% (1 mild reaction; 95% CI, 0.09%–18.9%) overall with no difference in patients with (6.3% [1/16]; 95% CI, 0.15%–28.7%) or without (0%; [0/11] upper bound 95% CI, 25.0%) corticosteroid premedication.

Summary of study's conclusions – Iodine-based contrast media

Use of premedication with antihistamine (OR, 0.5; P = .01) was preventive against recurrent HSR (Cha, 2019). A change in the culprit ICM and premedication with antihistamine are useful for reducing the recurrence of HSRs (Cha, 2019).

Accelerated intravenous premedication with corticosteroids beginning 5 hours before contrast-enhanced CT has a breakthrough reaction rate noninferior to that of a 13-hour oral premedication regimen (Mervak, 2017).

In patients with moderate-to-severe HSR, steroid premedication only shows limited effectiveness. Steroid premedication did not result in improvement of the overall outcomes at the subsequent re-exposure (16.5% vs. 23.0%, P = 0.250). Steroid premedication did not show protective effects against recurrent HSR (Park, 2017).

Premedication with an antihistamine had a significant recurrence-lowering effect (OR, 0.569; 95% CI: 0.443, 0.731; P=.001) in mild HSR (Park, 2018).

Premedication with cetirizine and prednisone before radiologic procedures, regardless of dosage of the corticosteroid, proved to be efficient in patients with a history suggesting hypersensitivity to iodine-based contrast media (Specjalski, 2020).

Summary of study's conclusions – Gadolinium-based contrast agents

Premedication with antihistamine and corticosteroid does not eliminate moderate or severe reactions to gadobenate dimeglumine and recurrent reactions can be of greater severity than index reactions (Bhatti, 2018).

Both premedication protocols (antihistamine, systemic steroid plus antihistamine) did not show a recurrence-lowering effect, compared with the non-premedicated cases (antihistamine administration [OR, 1.180; 95% CI, 0.647–2.154; P = 0.589] and systemic steroid plus antihistamine [OR, 1.668; 95% CI, 0.609–4.565; P = 0.316]) (Ryoo, 2019).

Empirically switching GBCAs, with or without the use of corticosteroid premedication, can substantially reduce the rate of hypersensitivity breakthrough reactions (Walker, 2021).

Level of evidence of the literature
The quality of certainty of evidence for the outcome allergic / hypersensitivity reaction was downgraded from low to very low due to risk of bias (as described below), heterogeneity of included studies, indirectness, and imprecision of outcome measures (low numbers of events).

The risk of bias of the included studies was deemed high due to high risk of bias in selection of participants, selection of the outcome of interest and Confounding analysis.

## Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: What are the effects of prophylactic measures to prevent hypersensitivity reactions after contrast media administration?

**P** (Patients): Patients undergoing radiological examinations with contrast media.
**I** (Intervention): Prophylactic measure to prevent hypersensitivity reactions after contrast administration.
**C** (Comparison): No prophylactic measure or a different prophylactic measure to prevent hypersensitivity reactions after contrast administration.
**O** (Outcome): Allergic reactions to contrast media, hypersensitivity reaction, type I/type IV, severe allergic reaction.

Relevant outcome measures
The working group considered *allergic / hypersensitivity reactions to contrast* as critical outcome measures for the decision-making process.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until April 22nd, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 400 hits. Studies were selected based on the following criteria

- Adult patients undergoing radiological examinations with contrast media.
- Evaluation of effectiveness of prophylactic measures to prevent hypersensitivity reactions after contrast administration.
- Reports predefined outcome measure: hypersensitivity reactions.
- No reports of case series or exploratory findings (n ≥ 10).

Based on title and abstract a total of twenty-three studies were selected. After examination of full text, a total of fifteen studies were excluded and eight studies were included in the literature summary. Reason for exclusion is reported in Table of excluded studies in the Appendices to modules.

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 : 28-11-2022

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

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# Hypersensitiviteitsreacties na niet-vasculaire CM

## Uitgangsvraag

Welke profylactische maatregelen zouden moeten worden genomen bij patiënten met een verhoogd risico op hypersensitiviteitsreacties na niet-vasculaire contrastmiddeltoediening?

## Aanbeveling

Kleine hoeveelheden van ICM of GBCA kunnen worden geabsorbeerd door mucosa en dringen door tot de systemische circulatie na alle typen niet-vasculaire CM-toediening.

Hypersensitiviteitsreacties na niet-vasculaire CM-toediening van ICM of GBCA kunnen voorkomen, maar hun incidentie is laag tot zeer laag.

Geen preventieve maatregelen zijn geïndiceerd voor ERCP of voor niet-vasculaire GBCA-toediening.

Voor andere indicaties van ICM kan geen duidelijke aanbeveling worden gegeven voor patiënten die in het verleden een hypersensitiviteitsreactie na contrasttoediening hebben gehad.

Bij patiënten die een ernstige hypersensitiviteitsreactie na contrasttoediening hebben gehad, dient de mogelijkheid van alternatieve beeldvorming of contrastmiddel te worden overwogen samen met een radioloog, en een strikte indicatie voor het gebruik van niet-vasculaire CM toediening is noodzakelijk.

Bij patiënten die een ernstige hypersensitiviteitsreactie na contrasttoediening hebben gehad kunnen de preventieve maatregelen zoals beschreven in *module 3.5.4 Profylactische maatregelen om hypersensitiviteitsreacties na CM te voorkomen* worden gevolgd vooraf aan het onderzoek met niet-vasculaire CM-toediening. Indien mogelijk na laboratorium- en huidtesten door een specialist in geneesmiddelovergevoeligheid.

## Overwegingen

1. Gastro-intestinal administration

*Barium sulphate* suspensions are used more and more infrequently in fluoroscopy than in the 1970 and 1990s. Commercial barium sulphate suspensions are inert and not absorbed by the gastrointestinal mucosa. Trace amounts of barium ions may be absorbed by mucosa and stored in soft tissue or bone (Skucas 1997). Hypersensitivity reactions to barium sulphate are exceedingly rare and are usually mild. They have been estimated to occur in about 1 : 1,000,000 cases (Janower, 1986). Yet, severe reactions have been published as case reports in the heyday of barium use, but are exceedingly rare (Seymour, 1997).

It is probable that hypersensitivity reactions are not true reactions to barium sulphate but rather to additives of the commercial barium preparations such as methylparaben or carboxymethylcellulose. In addition, they may also be attributed to the use of glucagon in upper or lower GI studies (Gelfand, 1985).

*Iodine-based contrast media* (ICM) are widely used in CT to opacify and/or distend the stomach and bowel structures, either via oral intake, via a nasogastric or nasoduodenal tube, or via direct rectal administration. The use of fluoroscopy of the GI system is rapidly declining. The use of (CT) fistulography for entero-cutaneous fistula is also included here.

For high-density (positive) contrast, the older high-osmolar ionic ioxithalamate meglumine and sodium meglumine amidotrizoate are still widely used for this purpose. In CT, water or low-density (negative) CM (Mannitol or PEG) are used more frequently.

In contrast to barium sulphate, small amounts of iodine-based CM are absorbed by the gastro-intestinal mucosa (in the order of 0 to 2%) (Sohn, 2002), with relatively more absorption in the upper than in the lower gastrointestinal system. This absorption may be slow. Therefore, also iodine-based CM can elicit hypersensitivity reactions of all severities, both acute and delayed reactions (Miller, 1997; Schmidt, 1998; Davis, 2015; Böhm, 2017). There is no convincing data that inflammation or ischemia of bowel walls lead to more hypersensitivity reactions.

Angioedema may also occur in the small bowel and is often under diagnosed as it results in atypical abdominal discomfort (Chen, 2012; Hu, 2012). It is probably more frequently caused by intravascular ICM and GBCA administration, and may be mediated via the gut-associated lymphoid tissue (GALT) in the bowel wall (Böhm, 2017).

Because iodine-based CM in CT is usually administered intravenously and orally, the true incidence of gastro-intestinal CM administration is difficult to determine. As published cases are limited to case reports, the incidence is probably very low, much lower than the incidence after intravascular iodine-based CM administration.

*Gadolinium-based contrast agents* (GBCA) are only rarely used for gastrointestinal use in everyday practice. These GBCA can be absorbed by gastro-intestinal mucosa in small amounts. Given the very low incidence of hypersensitivity reactions to intravascular GBCA, the risk of hypersensitivity reactions is largely theoretical.

2. Urogenital administration

*Iodine-based contrast media* are used for a variety of fluoroscopic urologic procedures such as cystography, pyelography, nephrostomography, urinary diversions and neobladders, urodynamic examinations, or retrograde urethrography.

As in gastro-intestinal applications, the urothelium can also absorb these CM in small amounts (Davis, 2015), with a potentially higher rate if CM is injected under pressure or if drainage of CM is slow. Therefore, urologic administration can elicit hypersensitivity reactions of variable severity (Weese, 1993; Miller, 1995), even breakthrough reactions (Armstrong, 2005). As shown by one large published series and selected case reports, the incidence of reactions is low (Cartwright, 2008). Nevertheless, in a recent survey with a low response rate by members of the Society of Endourology, hypersensitivity reactions were reported by a considerable number of selected respondents during their careers (Dai ,2018).

In hysterosalpingography the incidence of hypersensitivity reactions following use iodine-based CM is very low, even after venous intravasation (Sanfilippo, 1978; Lindequist, 1991; La Fianza, 2005).

*Gadolinium-based contrast agents* are virtually never used directly for urogenital procedures and no data on hypersensitivity is available.

3. Biliary system administration
*Iodine-based contrast media* are mainly used during diagnostic or interventional endoscopic retrograde cholangiopancreatography (ERCP) and in percutaneous transhepatic cholangiography (PTC) with or without drain (PTCD) placements.

There is some systemic absorption of CM after ERCP in the biliary tract, in which the contrast can be detected in the kidneys afterwards. Therefore, also biliary procedures may elicit hypersensitivity reactions to iodine-based CM. However, as shown in the largest published series, the incidence of hypersensitivity reactions during ERCP is very low, even in high-risk patients (Dragonov, 2008; Trottier-Tellier, 2018).

*Gadolinium-based contrast agents* are virtually never used directly for biliary procedures and no data on hypersensitivity is available.

4. Intra-articular administration
*Iodine-based contrast media* are frequently used for arthrography, single/double-contrast CT arthrography or to help guide needle placement in MR Arthrography.

The intra-articular contrast can be absorbed in small amounts by the synovium. Hypersensitivity reactions have been described with severe reactions occurring in incidental patients (Newberg, 1985; Westesson, 1990; Hugo III, 1998). However, in two large surveys of 126,000 and 262,000 arthrograms the risk of hypersensitivity reactions was low, and most reactions were mild (Newberg, 1985; Hugo III, 1998).

*Gadolinium-based contrast agents* are used for MR arthography in a very diluted amount (2 mmol/L or a 1:250 dilution).

Similar to iodine-based CM, trace amounts of GBCA can be absorbed by synovium. However due to the dilution the number of hypersensitivity reactions following MR arthrography is almost non-existent (Schulte-Altedorneburg, 2003).

5. Miscellaneous
*Iodine-based contrast media* are or have been used for a number of miscellaneous procedures like (CT) discography, sialography, et cetera.

Hypersensitivity reactions in most of these procedures are not documented well enough to discuss them in this guideline, or have fallen in disfavour.

## Onderbouwing

## Achtergrond

There was few good data to structurally search and critically assess the literature on hypersensitivity reactions after nonvascular contrast media (CM) administration, such as gastro-intestinal administration, urogenital administration, intrabiliairy administration, and intra-articular administration.

Therefore, the guideline committee decided that it was more appropriate to provide an expert-opinion review of the available literature separately and to try to provide recommendations for practice.

## Verantwoording

Laatst beoordeeld : 24-06-2020

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

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# GBCA

## Verantwoording

Laatst beoordeeld :

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

# Risicofactoren en preventie van NSF

## Uitgangsvraag

a) Welke patiënten hebben en verhoogd risico op het ontwikkelen van Nephrogenic Systemic Fibrosis (NSF)?
b) Welke maatregelen zijn nodig om NSF te voorkomen?

## Aanbeveling

Gebruik laag-risico (ionisch en non-ionisch) **macrocyclische** GBCAs voor medische beeldvorming bij alle patiënten. Lineaire GBCA is geassocieerd met NSF, daarom dient **lineaire** GBCA enkel overwogen te worden indien een macrocyclisch GBCA de diagnostische vraag niet kan beantwoorden.

Maak een individuele risico-voordeel analyse met de aanvragend arts van de patiënt en met een nefroloog om verzekerd te zijn van een strikte indicatie voor MRI met **lineaire** GBCA bij patiënten met eGFR < 30 ml/min/1.73m*2*.

Voor preventie van NSF bij patiënten die al afhankelijk zijn van hemodialyse of peritoneale dialyse, hoeft de toediening van **macrocyclische** GBCA niet direct gevolgd te worden door een hemodialyse sessie.

Om de hoeveelheid circulerend GBCA te minimaliseren, dient bij patiënten die al chronische hemodialyse ondergaan de toediening van **lineaire** GBCA direct te worden gevolgd door een (high-flux) hemodialyse sessie, wat herhaald wordt in de twee opeenvolgende dagen.

Bij predialyse patiënten (eGFR<15 ml/min/1.73m*2*) en peritoneaal dialyse patiënten dient het risico op NSF door **lineaire** GBCA te worden afgewogen tegen het risico van het plaatsen van een tijdelijke centraal veneuze toegang voor hemodialyse.

## Overwegingen

<u>Prevalence and risk of NSF and type of GBCA</u>
The majority of histology proven NSF cases has been described between 1997 and 2007, which largely consisted of cases with a temporal relation with high dose linear gadolinium-based contrast agent (GBCA) administrations (Attari, 2019). Several meta-analysis have shown a positive correlation between GBCA and NSF, predominantly based on studies using linear GBCA (Agarwal, 2009; Zhang, 2015). The risk of NSF relate to the administered dose and physiochemical characteristics of GBCAs, including pharmacodynamic stability, kinetic stability, and the amount of excess ligand (Khawaja, 2015).

In a risk-factor analysis of 370 biopsy-proven published NSF cases following use of linear GBCA it was concluded that reductions in risk may be attained with: 1) avoiding high doses of GBCA (> 0.1 mmol/kg); 2) avoiding nonionic linear GBCA in patients undergoing dialysis and patients with eGFR < 30 ml/min/1.73m$^2$, especially in the setting of pro-inflammatory conditions; 3) dialyzing quickly after GBCA administration for patients already on dialysis; and 4) avoiding GBCA in acute renal failure (Zou, 2011).

By combining pharmacovigilance (Food and Drug Administration Adverse Event Reporting System (FAERS)) and legal databases, a total of 382 biopsy-proven, product-specific cases of NSF were analysed. Of these, 279 cases were unconfounded and all involved a linear GBCA, nonionic more than ionic, and most frequently gadodiamide. No unconfounded cases were found for gadoteridol or gadobenate (Edwards, 2014).

A very recent study based on a legal database containing biopsy-proven, unconfounded NSF cases has estimated that a total of 197 and 8 cases have been reported for the linear GBCAs gadodiamide and gadoversetamide, respectively. Estimated incidences of NSF based on the FAERS analysis are 13.1/million and 5.0/million administrations for the linear non-ionic GBCAs gadodiamide and gadoversetamide worldwide (Semelka, 2019).

Considering the hypothesized pathophysiology of NSF involving free circulating gadolinium ions, macrocyclic GBCAs are considered to have a higher thermodynamic and kinetic stability and thus less associated with the risk of NSF (Sherry, 2009).

The prevalence of NSF after use of macrocyclic GBCA is very low. No cases of NSF have been found in large studies using gadobenate (Bruce, 2016), gadobutrol (Michaely, 2017), and gadoteridol or gadobenate (Soulez, 2015). Using the Girardi criteria for diagnosis, the worldwide total number of unconfounded cases for gadobutrol is 3 (Elmholdt, 2010; Endrikat, 2018), while there were no cases for gadoteridol (Reilly, 2008; Edwards, 2014), or gadoterate (Soyer, 2017).

In addition, there have been no unconfounded cases reported for the hepatobiliary linear GBCA gadobenate (Edwards, 2014) and gadoxetate (Endrikat, 2018). Patients with chronic liver diseases that are awaiting or undergoing liver transplantation are no longer consider to be an independent risk factor for NSF (Smorodinsky, 2015).

On March 17, 2016, the European Medicines Agency (EMA) initiated a review of the risk of gadolinium deposition in brain tissue following the repeated use of GBCAs in patients undergoing contrast-enhanced MRI scans. Following an in-depth review, the EMA issued its final recommendations on July 21, 2017, endorsed by the European Commission on November 23, 2017, and now applicable in all EU Member States limiting the use of GBCAs to macrocyclic GBCAs and restricting the use of linear GBCAs to selected indications, such as hepatobiliary MRI or MR arthrography (EMA, 2017; Dekkers, 2018). See Table 1 for overview of GBCAs and recommendations of the EMA.

**Table 1 Overview of available GBCAs and the EMA recommendation (Dekkers, 2018)**

| | | | | |
|---|---|---|---|---|
| Gadopentetate | DTPA | Linear | Ionic | **Suspend (maintain for intra-articular injections only)** |
| Gadobenate | BOPTA | Linear | Ionic | **Restrict to liver scans** |
| Gadoxetate | EOB-DTPA | Linear | Ionic | Maintain (for liver scans) |
| Gadodiamide | DTPA-BMA | Linear | Non-ionic | **Suspend** |
| Gadoversetamide | DTPA-BMEA | Linear | Non-ionic | **Suspend** |
| Gadoterate | DOTA | Macrocyclic | Ionic | Maintain |
| Gadoteridol | HP-DO3A | Macrocyclic | Non-ionic | Maintain |
| Gadobutrol | BT-DO3A | Macrocyclic | Non-ionic | Maintain |

Considering these new regulations, previous perceived risks for NSF based on linear GBCAs should be differentiated from the risks that apply to macrocyclic GBCAs. From the data currently available, for the GBCA currently allowable in Europe the risk of NSF is extremely low, even in patients with eGFR < 30 ml/min/1.73m$^2$ and patients on dialysis.

Haemodialysis to prevent NSF

Several studies have been performed to investigate the dialysability of GBCAs. These studies have shown that a single haemodialysis session can remove around 65-97% of circulating GBCA, whereby success depends on dialysis technique (high flux, large pore membranes (Ueda 1999)). Approximately 98% is eliminated after three consecutive dialysis sessions (Joffe 1998; Tombach 2002; Gheuens 2014). Based on these data, early haemodialysis would be an effective treatment for preventing NSF. However, this hasn't been proven. For example, a retrospective chart review described ten haemodialysis patients who developed NSF after administration of GBCA. In none of these patients, immediate haemodialysis after injection with GBCA could prevent NSF (Broome 2007).

Based on the dialysability of GBCAs and the fact that NSF is a potential lethal condition, many guidelines recommend scheduling GBCA administration shortly before the next haemodialysis session (ACR Manual 10.3; ESUR Guideline v10).

Peritoneal dialysis does not effectively remove gadolinium (Rodby 2018). However, instituting haemodialysis in a peritoneal dialysis patient without a functioning vascular access goes with a significant risk, as it is an invasive treatment that requires placement of a temporary haemodialysis catheter. The same accounts for predialysis patients (eGFR<15 ml/min/1.73m$^2$).

## Onderbouwing

## Achtergrond

Nephrogenic systemic fibrosis (NSF) is a very rare, idiopathic, progressive, systemic fibrosis disease that has been associated with renal insufficiency and could result in significant disability due to scleromyxedema-like cutaneous manifestations and mortality. Since there is currently no consistently effective treatment, NSF prevention would be essential, ideally by confirming risk factors for the disease.

Risk factors for NSF

Little is known about the pathophysiology of NSF and it has been postulated that the deposition of free gadolinium causes fibrous connective tissue formation (Ting, 2003). It has been described to occur after exposure to linear gadolinium based contrast agents (GBCA) in particular. Literature published prior to 2007 has not only suggested that free gadolinium, particularly gadodiamide, is a trigger of NSF, but has reported a strong causal relationship between gadolinium exposure and the development of NSF (Thomsen, 2016). However, this association may be affected by other factors or cofactors, such as dosage or type of GBCA, dialysis modality, renal disease severity, liver transplantation, chronic inflammation, or accelerated atherosclerosis.

Prevention of NSF

Several measures to prevent the development of NSF can be taken. As such, the use of high risk and high dose GBCAs should be avoided. An alternative to scanning with GBCA is to scan with the use of iodinated contrast media, however this carries the risk of post-contrast acute kidney injury (see Module 6). Since the connection between NSF and GBCA has become known, changes in CM administration protocols with lower GBCA concentration and use of macrocyclic GBCAs has led to a decrease in NSF incidence. Reports are showing virtually no new NSF cases since 2008 in both patients with normal renal function and patients with renal impairment, in spite of continued use of GBCA, albeit at lower doses and by using preferentially the macrocyclic preparations.

## Conclusies / Summary of Findings

| | |
|---|---|
| **Very low GRADE** | There seems to be no association between co-morbidities (history of hypothyroidism or deep venous thrombosis, and dependent oedema) and risk of nephrogenic systemic fibrosis in patients on dialysis receiving linear GBCAs.<br><br>*Source: (Kallen, 2008))* |

## Samenvatting literatuur

*Research question a: Risk factors for NSF*

Studies that assessed risk factors related to administration of type and dose of gadolinium-based contrast agents (GBCA) have been described in the module nephrotoxicity of gadolinium-based contrast agents. There was 1 additional study included investigating other potential factors associated to NSF. Kallen (2008) performed a matched case-control study (19 cases and 57 controls), however this study was restricted to linear GBCAs only. Participants were dialysis patients with and without a diagnosis of NSF treated at an academic medical centre.

Results

*Outcome- comorbidities*
In a multivariate analysis Kallen (2008) found no association between NSF and selected exposures (history of hypothyroidism (OR, 95% CI: 4.18 0.66 to 26.57); history of deep venous thrombosis (OR, 95% CI: 3.37 0.60-18.85), and dependent oedema (OR, 95% CI: 3.15 0.67 to 14.77).

Quality of evidence
The quality of certainty of evidence was downgraded from high to very low: downgraded by two levels due to imprecision (small number of patients), and indirectness (NB. only linear GBCAs were administered to the patients in the study which are no longer available on the European Market).

*Research question b: Prevention of NSF*
Not applicable. There were no studies investigating the research question and meeting the selection criteria.

## Zoeken en selecteren

Research question a: Risk factors for NSF
To answer the clinical question a systematic literature analysis was performed:
Search question: What factors are related to an increased risk on Nephrogenic systemic fibrosis?

**P** (Patient): Patients with reduced kidney function or other potential risk factors that are scheduled to receive intravascular contrast media.
**I** (Intervention): Patients with potential risk factors for NSF: Patient-related, pre-existing chronic kidney disease, Renal insufficiency, chronic CKD, Age 70 years and older, Liver transplantation, Liver failure, Kidney transplantation, Chronic inflammation, Atherosclerosis, Peripheral arterial disease, Dialysis, Renal replacement therapy, Diabetes Mellitus, type 1 or type 2, Congestive heart failure NYHA grade III-IV, Dehydration, Multimorbidity, Concurrent use of nephrotoxic medications: NSAIDs, Cox-2 inhibitors, ACE-inhibitor, ARB-blocker, other Dialysis modality (Peritoneal or haemodialysis), Recent dialysis shunt / PD catheter, Acidosis, EPO use, Dose of contrast and type of contrast (GBCA).
**C** (Comparison): Patients without potential risk factors for NSF.
**O** (Outcomes): Frequency of NSF, systemic fibrosis, scleroderma, dialysis-associated systemic fibrosis.

Relevant outcome measures
The working group considered nephrogenic systemic fibrosis as a critical outcome measure for the decision making process.

Methods
The databases Medline (OVID) and Embase were searched from January 2000 till February 23th 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS).

The literature search procured 228 hits: 22 SR, 20 RCTs and 186 OBS. Based on title and abstract a total of 20 studies were selected. After examination of full text 19 studies were excluded and 1 study involving linear GBCAs was included in the literature summary. No studies were identified involving macrocyclic GBCAs, which are currently the only agents available in the European market.

*Research question b: Prevention of NSF*
To answer the clinical question a systematic literature analysis was performed for the search question: What is the effect of the different measures to prevent nephrogenic systemic fibrosis in patients who have an increased risk of developing nephrogenic systemic fibrosis and who receive contrast with gadolinium?

**P** (Patient): Patients exposed to gadolinium-based contrast agents who have an increased risk of developing nephrogenic systemic fibrosis (NSF).
**I** (Intervention): Measures for prevention of NSF.
**C** (Comparison): No measures or other measures for prevention of NSF.
**O** (Outcomes): Nephrogenic Systemic Fibrosis (NSF), mortality.

Relevant outcome measures
The working group considered Nephrogenic Systemic Fibrosis (NSF) and mortality as critical outcome measures for the decision making process.

Methods
The databases Medline (OVID) and Embase were searched from January 1996 till March 23th 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS).

The literature search procured 142 hits. 7 SR, 10 RCTs, 43 OBS, and 82 other types of studies. Based on title and abstract a total of 29 studies were selected. After examination of full text all studies were excluded and no studies have definitely been included in the literature summary.

## Verantwoording

Laatst beoordeeld : 24-06-2020

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

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# Gadoliniumdepositie

Contents of chapter 9:

- Introduction to Safe Use of Gadolinium-Based Contrast Agents (updated)
- Module 9.1 Gadolinium deposition in the brain and body (updated)
- Module 9.2 Strategies for Dose Reduction of Gadolinium-Based Contrast Agents (new)

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

## Referenties

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# Introductie gadoliniumdepositie

*Disclaimer: This narrative review has been written by members of the Guideline Development Group so that non-specialized readers can follow the Modules about Hypersensitivity more easily. It was not part of the actual guideline process with structured literature analyses.*

Gadolinium-based contrast agents (GBCA) are routinely used in patients undergoing magnetic resonance imaging (MRI) to enhance image contrast and thereby improving detection and characterization of lesions. These agents exploit the highly paramagnetic nature of gadolinium (Gd), which alters the local magnetic properties shortening both T1 and T2 of tissue leading to increased signal intensity on T1-weighted images (and reduced signal intensity on T2-weighted images) (Elster, 2021). Since their introduction in 1988, an estimate of 700 million doses have been delivered and the current (end of 2021) estimated use is 50 million doses per year (Balzer, 2017; Endrikat, 2018, McDonald, 2018; Bayer AG estimates based on various internal and external data, 2022). Overall, 30--45% of the MRI scans have used GBCAs, with high contributions in current sales by Neuroradiology (~40%) and Cardiovascular Radiology (~20%) (Bayer AG estimates, based on various internal and external data, 2022).

## 1. Gadolinium Physicochemistry

Gadolinium and relaxivity

Gadolinium (Gd; Z = 64 and MW = 157,25 g/mol) is a rare earth metal from the Lanthanide family of elements in the periodic system. It has seven unpaired electrons in its 4f orbitals, has a high magnetic moment, and a very long electron spin relaxation time (Caravan, 1999; Hao, 2012; Lin, 2007).

The efficiency of T1-weighted contrast agents in aqueous solutions is determined by its relaxivity (R1 = 1 / T1). The relaxivity is determined by relaxation effects of water molecules interacting directly with the paramagnetic ion (inner sphere) and interactions with closely diffusing water molecules without interacting with the M-L complex (outer sphere).

For clinical GBCA 60% of relaxivity comes from inner sphere effects and 40% from outer sphere effects. Chelated gadolinium complexes are monohydrated ($Gd(H_2O)^{3+}$), as in their spherical configuration there is only enough space around the gadolinium for one (inner sphere) water molecule that exchanges rapidly with other nearby water molecules (outer sphere) (De Leon-Rodriguez, 2015).

Gadolinium chelation and stability constants

In biological systems, unchelated $Gd^{3+}$ ions are toxic because the ion has an ionic radius (107,8 pm) close to the ionic radius of $Ca^{2+}$ (114 pm) and can bind to $Ca^{2+}$ ion channels and $Ca^{2+}$-dependent proteins such as metalloenzymes or messenger proteins like calmodulin or calexitin.

To suppress this potential toxicity, the $Gd^{3+}$ ions must be tightly bound to an organic ligand to form a metal-ligand (ML) complex or chelate. The ligand will reduce toxicity, change the tissue distribution, and influence relaxivity. In the current European situation, such ligands are macrocyclic (DOTA, BT-DO3A or HP-DO3A) or

linear (BOPTA or EOB-DTPA) (Supplemental Table S2).

Normally, equilibrium exists for the reaction between metal M and ligand L. The reaction can be written as: (M) + (L) ↔ (ML)

The stability of the Gadolinium-ligand complex can be described by a number of constants.

The logarithm of the thermodynamic stability constant Ktherm describes the affinity of Gd for the ligand and is normally measured at pH = 14. Higher values imply a higher stability. Ktherm = (ML) / (M) · (L).

For biological systems more appropriate is the logarithm of the apparent or conditional thermodynamic stability constant Kcond, which considers the total concentration of the free ligand, including all its protonation states. It characterizes the affinity of Gadolinium for ligand in aqueous media under physiologic conditions (pH = 7,4). In all GBCA the conditional stability is substantially lower than the thermodynamic stability. Kcond = (ML) / (M) · {(L) + (HL) + (H2L) +..... }

The kinetic stability describes the kinetic rate of the dissociation of the Gadolinium-Ligand complex. It is closely related to the thermodynamic stability and is commonly described as the half-life of the dissociation of the Gd-Ligand complex or by the observed dissociation constant kobs. To be measurable, such kinetic analyses are done under acidic conditions at pH =1 (Port, 2008). Dissociation rate = kobs (ML).

Some commercial solutions of contrast media contain variable amounts of free ligands or calcium complexes to ensure chelation of any free Gd3+ or other metal traces from the vial during its shelf life. This amount is often used as indirect indicator of the instability of the compound.

The thermodynamic stability constants are a measure of how much uncomplexed Gd3+ will be released in biologic tissues if the system reaches equilibrium. In vivo, such new thermodynamic equilibrium is usually not reached as most of the complex is excreted long before any uncomplexed gadolinium can be released. Therefore, the kinetic stability is in vivo much more important than the thermodynamic stability.

Transmetallation

Transmetallation is the exchange between Gd3+ and other metal ions M+ that have greater affinity for the chelate. The amount of transmetallation depends on the stability of the chelating ligand. Gadolinium ions can be removed from the Gd-ligand complex by several endogenous positively charged ions like Zn2+, Cu2+, and Ca2+ whereby Gd3+ is released, while endogenous negatively charged ions like PO43- and CO32- can compete with the free ligand to form insoluble toxic Gd3+ compounds like GdPO4 or Gd2(CO3)3 (Idee, 2006).

Transmetallation can be described by the reaction: (Gd-L) + (M+) ↔ Gd3+ + (ML)

Of the most frequently described stability constants, a high kinetic stability is regarded as the most important to minimize transmetallation. Since the stability of the macrocyclic Gd chelates is much more limited by the slow release of Gd3+ from the complex, the kinetic stability is more important in such ligands.

The main physicochemistry and stability data of current GBCA are summarized in Supplemental Table S2.

Biodistribution and Elimination (see Module 10.1 for more details)
After intravenous administration, the GBCA is excreted by the kidneys with an early elimination half-life of about 1.5 h in patients with normal renal function. More than 90% of the injected GBCA is cleared from the body within 12 h. This early excretion phase is similar for linear and macrocyclic GBCA.

In patients with severely reduced renal function (eGFR < 30 ml/min/1.73m2) this elimination half-life for GBCA can increase up to 18-34 h (Joffe, 2008). During that time there is a potential for transmetallation with an increased release of free Gd3+ ions (Aime, 2009).

Recent systematic review of pharmacokinetic analysis revealed a deep compartment of distribution with long-lasting residual excretion. This long-lasting excretion is faster for macrocyclic compared to linear GBCA, correlated to the higher thermodynamic stability and differences in transmetallation. In addition, bone residence time for macrocyclic GBCA (up to 30 days) was much shorter than for linear GBCA (up to 2,5 years) (Lancelot, 2016).

## 2. Gadolinium Deposition in the Brain and Body (See Module 4.2.2 for update 2022)

A. Gadolinium Deposition in the Brain

*Clinical studies*
In 2014, it was suggested that the retrospectively observed hyperintensity of the dentate nucleus and the globus pallidus relative to the pons (dentate nucleus to pons (DNP) ratio) on unenhanced T1-weighted images of a population of patients with brain tumours, was related to repeated administrations of linear GBCAs (Kanda, 2014). Almost simultaneously, another group reported similar findings on unenhanced T1-weighted brain images after multiple injections of gadodiamide in patients with multiple sclerosis and patients with brain metastases (Errante, 2014).

After these initial reports, a multitude of retrospective studies have found increased SI in the dentate nucleus and or globus pallidus for linear GBCA. No such increases were found for macrocyclic GBCA, even after large doses (Radbruch, 2015 and 2017; Ramalho, 2016). In a recent systematic review of these studies by the ESMRMB Gadolinium Research Evaluation Committee (now ESMRMB-GREC) it was shown that there was large variety in sequence type and evaluation methodologies (Quattrocchi, 2019).

One of the biggest problems is that increased SI ratios at unenhanced T1-weighted MRI are a poor biomarker for gadolinium deposition, as SI ratios do not have linear relationship with Gd concentration and are highly dependent on the MRI parameters used during acquisition. Absolute signal intensity (expressed in arbitrary units) in MRI depends on many MRI parameters such as field strength, sequence type/parameters, coil sensitivity/filling factor, coil tuning/matching drift, etc. Since little is known about which forms of gadolinium are present (speciation), signal intensities, or changes thereof, will not reflect true changes in gadolinium

content (McDonald, 2018; Quattrocchi, 2019).

*Preclinical studies*
Preclinical studies in rat brains have highlighted the importance of in vivo dechelation of Gd3+ ions from less stable GBCAs, regardless of the presence of a renal dysfunction and with a clear dose-effect relationship. All quantities were in the nmol per gram tissue range. They have also shown that differences exist in the amount of total gadolinium retained in the brain when comparing different GBCA compounds (Jost, 2016; Robert, 2015 and 2017; Smith, 2017).

To date it is unclear what forms are responsible for the T1w signal increase (gadolinium speciation). Recently, it was shown that for gadolinium in the rat brain 3 different chemical forms must be distinguished: intact chelate, gadolinium bound to macromolecules, and insoluble gadolinium salts (Frenzel, 2017). The intact chelates were found for both linear and macrocyclic GBCA, but the other forms only for linear GBCA. As precipitated gadolinium does not induce any change in MRI signal when excitated, it is likely that the gadolinium bound to macromolecules is responsible for the visible T1w hyperintensity in clinical MRI (Gianolio, 2017).

Well-conducted long-term animal studies demonstrated that for linear GBCA a large portion of gadolinium was retained in the brain, with binding of soluble gadolinium to macromolecules. For macrocyclic GBCA only traces of the intact chelated gadolinium were present with complete washout in time (Jost, 2019; Robert, 2018).

Intact GBCA does not cross the intact blood-brain barrier. It is now believed that GBCA can reach the CSF via the choroid plexus and ciliary body and can reach the brain interstitium via the glympathic system along perineural sheaths and perivascular spaces of penetrating cortical arteries. GBCA distributed into the cerebrospinal fluid cavity via the glymphatic system may remain in the eye or brain tissue for a longer duration compared to the GBCA in systemic circulation. The glympathic system may be responsible for deposition in linear GBCA as well as for GBCA clearance (Deike-Hofmann, 2019; Taoka, 2018).

B. Gadolinium Deposition in the Body

Most data mentioned below are all from preclinical studies in animals.

*Gadolinium deposition in bone*
Lanthanide metals (gadolinium, samarium, europium, and cerium) have long been known to deposit in bone tissue and have effects on osteoblasts and osteoclasts, but the exact mechanisms are not yet well understood (Vidaud, 2012).

Gadolinium deposits have been found in samples of bone tissues of humans at higher concentrations than in brain tissue after administration of linear and macrocyclic GBCA, whereby linear GBCA deposit 4 to 25 times more than macrocyclic GBCA (Darrah, 2009; Murata, 2016; White, 2006; Wang, 2015).

The bone residence time for macrocyclic GBCA (up to 30 days) is much shorter than for linear GBCA (up to 8 years) (Darrah, 2009; Lancelot, 2016). Bone may serve as a storage compartment from which Gd is later released in the body (Thakral, 2007). It is postulated that the long-term reservoir of gadolinium in bones might implicate that some patients with high bone turnover, such as menopausal women and patients with osteoporosis may be more vulnerable to gadolinium deposition (Darrah, 2009).

*Gadolinium deposition in skin*
Gadolinium depositions in skin have been demonstrated ever since the association of GBCA with nephrogenic systemic fibrosis in 2006. See also section on NSF.

In skin biopsies of NSF patients, gadolinium was found along collagen bundles but also as insoluble apatite-like deposits, suggesting dechelation (Sieber, 2009; Thakral, 2009). After linear GBCA, gadolinium deposits were found up to 40-180 times more frequently than after macrocyclic GBCA, histologic changes are more extensive, and products of dechelation of GBCA can be found (Haylor, 2012; Wang, 2015).

Recently, gadolinium has also been found in the skin of patients with normal renal function after high cumulative GBCA doses (Roberts, 2016). With normal renal function even a case of 'gadolinium-associated plaques' has been described, which suggest that gadolinium deposition in the skin after linear GBCA might give clinically relevant symptoms (Gathings, 2015).

*Gadolinium deposition in other organs*
Thus far, little is published about the effects of gadolinium deposition in other organs.

In a clinical study in the liver, gadolinium deposits have been associated with iron overload in the livers of paediatric stem cell transplantation patients with normal renal function, reacting well to iron dechelation therapy (Maximova, 2016).

Based on animal studies, it has been suggested that residual Gd is also present in tissues samples of kidney, liver, spleen, and testis (Celiker, 2018 and 2019; Di Gregorio, 2018; McDonald, 2017; Mercantepe, 2018; Tweedle, 1995; Wang, 2015) While deposition in the brain was only 2 to 7 µg Gd, the amounts in other organs varied 168 to 2134 µg Gd for kidney, 16 to 388 µg Gd for liver, and 18 to 354 µg Gd for spleen, all per gram of tissue. In all tissues the level was highest for the linear GBCA gadodiamide (McDonald, 2017).

*Self-reported clinical symptoms*
Thus far, gadolinium deposition has not been associated with clinical symptoms, except for NSF. Small online gadolinium toxicity support groups in USA have claimed that their members have manifested symptoms analogous to NSF and have prolonged excretion of Gd in urine following administration of GBCA. Surveys have shown variable symptoms that occur either directly or within 6 weeks of GBCA administration. Most reported symptoms are burning sensation and bone pain in lower arms and limbs, central torso pain, headache with vision/hearing changes, and skin thickening and discoloration (Burke, 2016; Semelka, 2016).

This complex of symptoms was coined “gadolinium deposition disease (GDD)”. The critical findings are the presence of gadolinium in the body beyond 30 days, combined with at least 3 of the following features, with onset after the administration of GBCA: i) central torso pain,
ii) headache and clouded mentation, iii) peripheral leg and arm pain, iv) peripheral leg and arm thickening and discoloration, and v) bone pain (Semelka, 2016).

Significant differences in gadolinium levels in bone and urine have been observed between individuals experiencing symptoms and those who are not (Lord, 2018). A large study with a control population found more new symptoms within 24 h after exposure to GBCA than after unenhanced MRI. From the GDD-like symptoms, only fatigue and mental confusion were more frequently reported after enhanced MRI, questioning the term GDD (Parillo, 2019).

## 3. The European Medicines Agency (EMA) ruling

In many European countries, the described association between NSF and exposure to linear GBCAs in 2006 has resulted in the fact that most hospitals switched early (2007 and onwards) to macrocyclic GBCA use only, in most cases gadoterate or gadobutrol. After the series of publications describing increased signal intensities in the brain nuclei on unenhanced T1-weighted imaging after multiple linear GBCA exposures and post-mortem studies revealing the presence of small amounts of gadolinium in neural tissues, the EMA instituted an article 31 procedure. Eventually, this led to the withdrawal of EU market authorizations of the high-risk linear GBCA gadodiamide and gadoversetamide, as well as restrictions on the use of gadopentetate (MR Arthrography only) and, gadobenate (liver imaging only) (Dekkers, 2018; EMA, 2017). Therefore, for general use in MRI only macrocyclic GBCA are available, while the linear GBCA gadoxetate and gadobenate are available for liver-specific MRI.

Gadolinium metabolism and deposition still has many knowledge gaps for which an international research agenda is important. The ACR/NIH/RSNA Meeting 2018 has made a good inventory where future research should be aimed at (McDonald, 2018).

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

# Gadoliniumdepositie in het brein en lichaam

## Uitgangsvraag

Wat is het effect van gadoliniumdepositie in de hersenen en in het lichaam?

## Aanbeveling

Op dit moment is er geen bewijs van klinische symptomen of schade door gadoliniumdepositie in de hersenen of het lichaam.

Zorg voor een strikte indicatie voor gadolinium-versterkt MRI en gebruik alleen EMA-goedgekeurde gadoliniumhoudende contrastmiddelen bij alle patiënten om potentiële gadoliniumdepositie te minimaliseren*.

Deze richtlijnwerkgroep ondersteunt de door de ACR Committee on Drugs and Contrast Media gesuggereerde terminologie 'Symptoms Associated with Gadolinium Exposure' voor zelfgerapporteerde symptomen door patiënten.

*Zie ook module 4.3.3 Strategieën voor dosisreductie bij *GBCA*

## Overwegingen

**Narrative literature analysis (see also Introduction)**
*Gadolinium Deposition in the Brain – Extracellular Linear GBCA*
The use of linear extracellular GBCA led to visible changes in signal intensity (SI) ratios and measurable Gd depositions in the rat, dog, and human brain (Davies, 2021; De Bevist, 2020; El Hamrani, 2020; Fretellier, 2019; Grahl, 2021; Koiso, 2019; Minaeva, 2020; Richter, 2020; Wang, 2019a) and in the anterior pituitary gland (Mallio, 2019). Most depositions were in perivascular foci in the DN and GP (Davies 2021), with evidence of co-localization to parenchymal iron (Minaeva, 2020).

The amount of deposition in rat brains occurred independent of age or sex (Fretellier, 2019). Local blood-brain barrier disruptions (e.g., radiotherapy) did not lead to an increase in deposition (Jost, 2019). Active inflammation showed higher Gd concentration in inflamed areas in mouse brains (Wang, 2019a), while the presence of diabetes led to lower brain concentrations (Wang, 2019b). There was a decrease in concentration over time in all brain regions, but long-term retention over 1 year occurred preferentially in the rat DN (El Hamrani, 2020).

The use of intra-articular gadopentetate did not lead to visible Gd-deposition in human brains (Bunnell, 2021).

*Gadolinium Deposition in the Brain – Hepatobiliary Linear GBCA*

The use of linear GBCA such as gadobenate and gadoxetate has been limited in the EU to hepatobiliary MRI indications. The approved standard dose of gadobenate is 0.05 mmol/kg, less than the dose of linear extracellular GBCA. However, outside the EU gadobenate is used for total body indications, in doses up to

0.1 mmol/kg. Use of gadobenate led to visible SI changes in human brain (Barisano, 2019; Nguyen, 2020). Neuroinflammation led to higher Gd concentrations in the rat brain after gadobenate use (Damme, 2020).

In human cadavers, the mean Gd concentration in brain was 3-6x higher for gadobenate compared to gadoterate, but washed out over time (Kobayashi, 2021). In sheep, the level of Gd retention 10 weeks after a single dose injection was 14-fold higher for gadobenate than for gadoterate (Radbruch, 2019).

A meta-analysis on Gd deposition of gadoxetate showed significant bias of the 5 included studies, and therefore presently available data on gadolinium deposition for gadoxetate is still incomplete (Schieda, 2020).

*Gadolinium Deposition in the Brain – Macrocyclic GBCA*

The administration of cumulative doses of macrocyclic GBCA did not lead to visible changes in T1 signal intensity (SI) or to changes in T1 relaxation times in rat and human brains in most studies (Bennani-Baiti, 2019; Deike-Hoffmann, 2019, Forslin, 2019, Fretellier, 2019, Hannoun, 2020; Neal, 2020), but not in all (Splendiani, 2020).

Quantitative susceptibility mapping showed a relation of susceptibility changes with the number of gadobutrol injections, but only for the GP (Choi, 2020).

In rat brains macrocyclic GBCA led to measurable Gd concentrations 1-5 weeks after administration, which were lower for gadoteridol compared to gadoterate and gadobutrol. The GBCA wash-out over time led to a 3-5-fold reduction from 1 to 5 weeks and was more rapid for gadoteridol. The levels at 5 weeks were in the order of 0.14-0.30 nmol Gd/g tissue (Bussi, 2020 and 2021).

*Speciation of Gadolinium deposition in the brain*

In speciation analyses in rat brains, the macrocyclic GBCA gadoterate was present exclusively as the intact GBCA. For the linear GBCA gadobenate and gadodiamide a combination of intact GBCA, complexes of dissociated $Gd^{3+}$ bound to ferritin, and $Gd^{3+}$ bound to other macromolecules was present. Incomplete column recovery suggested presence of labile complexes of dissociated $Gd^{3+}$ with endogenous molecules. In addition, Gd was present in insoluble amorphous spheroid structures of 100-200 nm. Gadolinium was consistently co- localized with calcium, phosphate, and oxygen, suggesting the structures composed of mixed Gd/Ca-phosphates (Strzeminska, 2021 and 2022).

*Gadolinium Deposition in the Abdominal Organs*

Like in the brain, administration of linear GBCA led to increased Gd concentrations in abdominal organs, like kidney and liver. In sheep, concentrations were 3-21x higher than for macrocyclic GBCA: for kidney 502 vs. 86 ng/g tissue, for liver 445 vs 21 ng/g tissue, and for spleen 72 vs 4 ng/g tissue. Gadodiamide concentrations were 879, 780 and 137 ng/g, gadobenate concentrations 179, 157 and 16 ng/g, and gadobutrol 86, 35 and 6 ng/g tissue, respectively. However, no tissue alterations were detected (Richter, 2021).

In the abdominal organs Gd was least retained after administration of gadoxetate, followed by gadobutrol and gadodiamide when clinically recommended doses were administered.
Most of the retained gadolinium was excreted within 4 weeks after GBCA administration (Oh, 2020).

Administration of macrocyclic GBCA led to measurable Gd concentrations in liver and kidney 4 weeks after administration, which were lower for gadoteridol compared to gadoterate and gadobutrol. The levels for liver ranged 0.36-1.22 nmol Gd/g tissue and for kidney 39-294 nmol Gd/g tissue (Bussi, 2020 and 2021).

*Gadolinium Deposition in the Bone and Skin*

In rat skin, macrocyclic GBCA led to measurable Gd concentrations 1-5 weeks after administration, which were lower for gadoteridol compared to gadoterate and gadobutrol. The levels in skin where initially high, but after washout levels at 5 weeks were in the order of 0.31-0.53 nmol Gd/g tissue (Bussi, 2020 and 2021).

In human cadavers, 80 days after last GBCA exposure the mean Gd concentration in bone and skin was 2.9-4.4x higher for gadobenate compared to gadoterate. Bone was the primary Gd retention site with levels of 23-100 ng/g tissue/mmol GBCA. Gadolinium elimination rate was high for skin (Kobayashi, 2021).

*Potential clinical symptoms of Gd deposition*

Despite the retention of Gd in various tissues, no histopathologic changes in rat brains could be found (Ayers-Ringler 2022), nor tissue alterations in MS patients (Kühn, 2022).

In addition, no effect on sensorimotor or behavioural functions could be demonstrated for either linear or macrocyclic GBCA in mice (Akai 2021) or humans (Vymazal, 2020). Gadolinium retention was not related to symptom worsening in relapsing MS patients (Cocozza, 2019).

However, for linear GBCA, pain hypersensitivity has been seen in rats (Alkhunizi, 2020). In MS patients, increased relaxation was associated with lower information-processing speed (Forslin, 2019) or may result in mild effects on cerebellar speech or verbal fluency (Forslin, 2019; Kühn, 2022).

*Self-reported symptoms of gadolinium deposition*

The ACR Committee on Drugs and Contrast Media has suggested alternative nomenclature for patients with a spectrum of self-reported symptoms and signs. These include neurologic, cognitive, musculoskeletal, and other non-specific complaints, and different cytokine levels. They suggest terming these Symptoms Associated with Gadolinium Exposure (SAGE), to standardize reporting. SAGE will need to replace older terms such as gadolinium deposition disease (GDD), gadolinium storage disease (GSD), and gadolinium storage condition (GSC) (McDonald, 2022).

In a clinical toxicology assessment of patients with potential ‘Gd toxicity’, none of the reported symptoms were likely to be caused by GBCA exposure (Layne, 2021).

SAGE patients may differ from normal controls in the level of cytokines and may differ in the response to chelation therapy. This suggests inflammatory, immunologic, or other physiological differences in patients with SAGE (Maecker, 2021).

*Chelation therapy for Gadolinium deposition*

Several chelating agents may influence the distribution of gadolinium after administration of linear GBCA (Acar, 2019). In rats, the chelating agent Ca-DTPA could induce a relevant urinary Gd excretion and reduce the amount of Gd in brain, but only after administration of gadodiamide (Boyken, 2019). In a study of SAGE patients Ca-DTPA could significantly increase urinary Gd excretion (Maecker, 2021). In contrast, Zn-DTPA administration could show no benefit of chelation therapy in rats after linear GBCA (Prybylski, 2019).

In patients with self-reported symptoms, there is no evidence that supports a link between gadolinium deposition and the development of clinical sequelae in patients with normal renal function. Caution should be exercised to use inappropriate chelation therapies for treatment of SAGE (Layne, 2020).

**Recommendations**

*Disclaimer: Most recommendations in this module focus not so much on actions to be taken, but rather to increase awareness of gadolinium deposition.*

| |
|---|
| To date, even though there is evidence that gadolinium is deposited in tissues, there is no evidence of clinical symptoms nor harm associated with gadolinium deposition in the brain and body. |

| |
|---|
| Ensure a strict indication for gadolinium-enhanced MRI and only use EMA-approved gadolinium-based contrast agents in all patients to minimize possible gadolinium deposition. |

| |
|---|
| This guideline committee supports the ACR Committee on Drugs and Contrast Media's suggested terminology of Symptoms Associated with Gadolinium Exposure (SAGE) for self- reported symptoms and signs. |

## Onderbouwing

### Achtergrond

In 2014, progressive unenhanced T1-weighted (T1w) signal intensity (SI) increases in the dentate nucleus (DN) and globus pallidus GP) in patients who received at least 6 doses of linear GBCA were observed (Kanda, 2014). This publication triggered a huge amount of research on this subject, but so far, no clinical correlates of gadolinium deposition have been found. In this module a narrative review of the recent data (2019-2022) on gadolinium deposition in the brain and body organs is presented. Recommendations for a sensible use of gadolinium in diagnostic MRI will be given to limit potential effects of gadolinium deposition that may not be known at the present date.

## Zoeken en selecteren

For this chapter it was decided not to perform a systematic literature analysis, and therefore no search question with PICO was formulated.

Search and select (Methods)
No systematic literature analysis was performed. Instead, the authors made an overview of all available literature from their own database and through cross referencing. A narrative literature analysis can be found below.

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

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# Strategieën voor dosisreductie van GBCA

## Uitgangsvraag

Op welke manier kan de dosis van gadoliniumhoudende contrastmiddelen worden geminimaliseerd zonder de diagnostische accuratesse te verminderen?

De volgende categorieën werden gedefinieerd:

1. Potentiële dosisreductiestrategieën voor neurobeeldvorming met gadoliniumhoudend contrastmiddel
2. Potentiële dosisreductiestrategieën voor cardiovasculaire beeldvorming met gadoliniumhoudend contrastmiddel
3. Potentiële dosisreductiestrategieën voor musculoskeletale beeldvorming met gadoliniumhoudend contrastmiddel
4. Potentiële dosisreductiestrategieën voor abdominale beeldvorming met gadoliniumhoudend contrastmiddel
5. Potentiële dosisreductiestrategieën voor mammabeeldvorming met gadoliniumhoudend contrastmiddel

## Aanbeveling

1. Potentiële dosisreductiestrategieën voor neurobeeldvorming met gadoliniumhoudend contrastmiddel

De resultaten van de LEADER-75 studie geven aan dat de dosis van gadoliniumhoudende contrastmiddelen (gadobutrol) kan worden gereduceerd tot 75% van de standaarddosering (0.075 mmol/kg lichaamsgewicht (equivalent aan 0.075 ml/kg lichaamsgewicht)) bij patiënten met verdenking op laesies in de hersenen.

Het gebruik van deep learning gebaseerde methoden voor dosisreductie van gadoliniumhoudende contrastmiddelen bij patiënten met verdenking op laesies in de hersenen kan op basis van de huidige literatuur niet worden aanbevolen.

2. Potentiële dosisreductiestrategieën voor cardiovasculaire beeldvorming met gadoliniumhoudend contrastmiddel

Beeldvorming met standaarddosering wordt aanbevolen bij patiënten met klinische indicaties voor de toediening van gadoliniumhoudende contrastmiddelen bij cardiale MRI.

MRA-technieken zonder contrastmiddel (v.b. time-of-flight MRA) zijn op grote schaal beschikbaar en kunnen worden gebruikt voor accurate evaluatie van de graad van stenose van de supra-aortale vaten.

ECG-gated MRA sequenties zijn op grote schaal beschikbaar en worden aanbevolen in plaats van lage dosis contrastmiddel-versterkte MRA technieken voor de evaluatie van aorta dimensies.

3. Potentiële dosisreductiestrategieën voor musculoskeletale beeldvorming met gadoliniumhoudend contrastmiddel

Beeldvorming met standaarddosering wordt aanbevolen bij patiënten met klinische indicaties voor de toediening van gadoliniumhoudende contrastmiddelen bij musculoskeletale MRI.

4. Potentiële dosisreductiestrategieën voor abdominale beeldvorming met gadoliniumhoudend contrastmiddel

*Prostaat*

Er is toenemend bewijs dat biparametrische protocollen (T2w + DWI) zouden kunnen worden gebruikt als alternatief voor multiparametrische (T2w + DWI + DCE) protocollen voor de detectie van prostaatkanker.

*Lever*

Beeldvorming met standaarddosering wordt aanbevolen bij patiënten met klinische indicaties voor de toediening van gadoliniumhoudende contrastmiddelen bij MRI van de lever.

5. Potentiële dosisreductiestrategieën voor mammabeeldvorming met gadoliniumhoudend contrastmiddel

Beeldvorming met standaarddosering wordt aanbevolen bij patiënten met klinische indicaties voor het toedienen van gadoliniumhoudende contrastmiddelen bij MRI van de mammae.

## Overwegingen

### Narrative literature analysis

Gadolinium reduction strategies for neuroimaging

Most studies published on Gd reduction strategies are primarily focused on static contrast- enhanced (CE) T1-weighted (T1w) imaging. Several studies have compared the use of half- dose imaging (e.g., 0.05 mmol/kg body weight) to full dose (e.g., 0.1 mmol/kg body weight) imaging in neuro MRI protocols. Initial studies compared the diagnostic certainty of detecting brain metastasis for different doses of GBCA. These have shown that for spin-echo MR imaging high dose GBCA was an efficient way to improve the detection of brain metastases, in particular of small metastases (Åkeson, 1995). However, other studies in the same period showed that half dose imaging with magnetization transfer did not lead to significant differences in contrast enhancement for extra-axial tumours (e.g. meningiomas) upon visual inspection when compared with standard dose imaging (Haba, 2001; Han, 1998).

At 3.0 T half-dose imaging using gadopentetate has shown to yield in significantly higher contrast-to-noise ratio (1.3-fold higher) compared to full-dose imaging at 1.5 T (Krautmacher, 2005). However, it should be not that the older studies addressing half dose imaging such as the 1995 study by Åkeson used linear GBCA's which are currently no longer on available on the European Market because of suspended marketing

authorizations due to the potential risk of gadolinium retention in the human body (Åkeson, 1995). This also applies to the study by Khoury Chalouhi et al. which performed an intraindividual and interindividual comparison between 0.075 mmol/kg and 0.1 mmol/kg of gadoterate meglumine for cranial MRI because of the higher relaxivity of this GBCA agent (Khoury Chalouhi, 2014). Also two recent studies evaluated the use of half dose imaging of the high- relaxivity linear GBCA gadobenate dimeglumine decmonstrated that half dose compared to full dose imaging was non-inferior with regard to visual lesion delineation, internal morphology, and contrast enhancement at 1.5 T and 3.0 T (DeLano, 2021), and small or ring- enhancing metastases can be better visualized on half-dose gadobenate dimeglumine delayed CE T2 FLAIR for than on half dose CE-T1w brain MRI scans (Jin, 2021). It should be noted that the findings of studies on linear GBCA's cannot be extrapolated to the macrocyclic GBCAs that are currently used in neuroimaging because of the restricted use within the EU.

With regard to macrocyclic agents, the literature on reduced contrast dose is still limited and mainly based on the recent findings of the LEADER-75 trial. The LEADER-75 trial is an international prospective multicentre open-label crossover study that evaluated the use of three-quarter dose high-relaxivity gadobutrol (0.075 mmol/kg) compared with standard- dose gadoterate (0.1 mmol/kg) in adults with known or suspected CNS pathology undergoing CE brain imaging at 1.5T and 3T (Liu, 2021). Efficacy analysis in 141 patients found that improvement of reduced-dose gadobutrol over unenhanced images was noninferior to improvement of standard-dose gadoterate over unenhanced images. The authors used a 20% noninferiority margin for three primary efficacy measures using mean
readings ($p \leq 0.025$). The total number of lesions detected by mean reading was 301 for reduced-dose gadobutrol versus 291 for standard-dose gadoterate. The sensitivity (58.7%), specificity (91.8%), and accuracy (70.2%) for malignancy from majority reading were identical for reduced-dose gadobutrol and standard-dose gadoterate. No differences in mean reader confidence (3.3 ± 0.6 for both reduced-dose gadobutrol and standard-dose gadoterate) and reader preference were found (95% CI, -0.10 to 0.11). Albeit that the LEADER-75 trial is the first study to demonstrate convincing evidence for reduced dose imaging for macrocyclic GBCA in neuroimaging with out compromising reader confidence and reader preference, there are several knowledge gaps that remain. These include the potential influence of field strength, the potential differences in CE in CNS pathologies that were underrepresented in the LEADER-75 sample (e.g. 41% of the sample consisted of meningiomas and 24% of metastases), and influence of sequence design and acquisition.

In addition to static CE-T1W for brain imaging, reduced dose imaging has also been investigated for brain perfusion using dynamic susceptibility contrast (DSC). In DSC half dose imaging has shown to lead to a more accurate arterial input function (Filice, 2017) and CBV maps of comparable diagnostic quality as the corresponding images acquired with a full dose imaging (Crisi, 2017). However, in acute stroke half-dose DSC imaging was found to result in poor image quality in 40.7% of the cases receiving half-dose GBCA (0.1 ml/kg gadobenate dimeglumine body weight) vs. 6.3% of patients who received full GBCA dose (0.2 ml/kg gadobenate dimeglumine body weight), and may thus adversely affect stroke patient triage for thrombectomy (Heit, 2021). For DSC MRI in neuroimaging the field dependency remains to be investigated, and reduced dose imaging for this application remains controversial.

More recently, several recent studies have evaluated the clinical performance of deep learning (DL)–based methods for brain MRI reducing contrast dose up to 10-fold (Gong, 2021). However the missing enhancement

in small lesions indicates the need for further improvements in DL based algorithms or dosage design (Ammari, 2022; Luo, 2021). To date, DL strategies to minimize the dosage of GBCAs in brain MRI are still in its infancy and additional studies on the (potential) loss of diagnostic information are warranted.

Beyond reducing GBCA dose, the omission of the need of GBCA-based sequences in MRI scan protocols is also widely studied, in particular for the follow-up of extra-axial brain masses. The majority of the studies have focused on vestibular schwannomas, including evaluation of the diagnostic accuracy of non-CE gradient-echo constructive interference in steady state (CISS) and coronal T2w imaging in the setting of screening (Abele, 2014). A recent meta-analysis evaluated non-CE imaging for diagnosis and monitoring of vestibular schwannomas (Kim, 2019). In this meta-analysis six studies evaluated measurement difference, five articles focused on diagnostic accuracy and eight studied adverse effects. The studies showed that a non-CE MRI scan protocol with T2w imaging is highly accurate and highly reliable for diagnosing and monitoring vestibular schwannoma in comparison with CE-T1w imaging. In addition to vestibular schwannomas, also for meningiomas it has been shown that dimensions measured on pre-contrast T2 have similar results compared to measurements on CE-T1w imaging (Rahatli, 2019). One study leaving out CE-sequences in MRI protocols in children (Marsault, 2019). This study investigated the use of non-CE MRI for the follow-up of optic pathway gliomas in children, suggesting that tumour volume variation may be sufficient to assess optic pathway glioma progression (Marsault, 2019).

In addition to extra-axial masses, another disease group in which comparative studies on non-CE versus CE MRI protocols have been evaluated is multiple sclerosis. For multiple sclerosis three studies have evaluated the use of MRI protocols using non-contrast sequences for the detection of new brain lesions on follow-up imaging (Eichinger, 2021). These studies indicate that considering the very low incidence rate of new enhancing lesions in patients with non-progressive disease on follow-up, the routine administration of contrast in follow-up MRI scans is of limited value and does not change the diagnosis interval of disease progression. Finally, one study was identified that compared the use of non-CE MRI protocols to protocols using GBCAs for stroke. This study evaluated non-CE MR venography compared to conventional CE-T1w imaging and 3D gradient echo CE-T1w imaging, demonstrating that unenhanced MR venography had slightly lower sensitivity, specificity and accuracy for detecting cortical venous and/or dural sinus thrombosis (Sari, 2015) compared to the contrast-enhanced protocols.

Gadolinium reduction strategies for cardiovascular imaging

*Thoracic aorta*

Sequence designs such state-state free pression (SSFP) that enable combining non-breath- hold acquisitions with cardiac gating and respiratory triggering are widely used for vascular imaging with high resolution and high contrast between blood in the aorta and coronaries compared to surrounding tissue (Amano, 2008; Deshpande, 2001; François, 2008; Krishnam, 2008). International joint-society guidelines in the field of cardiology, cardiothoracic surgery and imaging have stated that non-CE MRA and CE-MRA are both acceptable imaging studies to measure the aorta in patients with thoracic aorta disease and adults with congenital heart disease (Baumgartner, 2010; Hiratzka, 2016). Direct comparison between non-CE MRA

to CE-MRA for the assessment of the dimensions of the thoracic aorta has been performed in several studies demonstrating that diagnostic image quality can be achieved without the need for Gadolinium (Bannas, 2013; Groth, 2012; Pennig, 2021; Veldhoen, 2017; Von Tengg-Kobligk, 2009).

*Supra-aortic vasculature*

Several studies have compared various non-CE MRA techniques for blood flow-related luminography, such as gradient-echo based time-of-flight (ToF), with CE-MRA for evaluating stenosis of the supra-aortic arteries. These studies show that non-CE MRA techniques are promising alternatives for stenosis grading, in particular for distinguishing surgically treatable internal carotid artery stenosis, without significantly compromising image quality or diagnostic accuracy (Babiarz, 2009; Lim, 2008; Liu, 2019; Peters, 2019; Zhang, 2020).

With regard to half dose imaging, half-dose (0.05 mmol/kg body weight) CE MRA and full- dose (0.1 mmol/kg body weight) CE-MRA have been evaluated with regard to SNR, CNR at both 1.5 T and 3T, demonstrating that dose-reduction of cervical CE-MRA is feasible at 3T without compromising angiographic quality with regard to stenosis evaluation (Dehkharghani, 2015). Low dose time-resolved CE-MRA has been evaluated compared to non-contrast ToF MRA and high-resolution CE-MRA, showing that time-resolved MRA has a good image quality and accurate stenosis grading compared to high-resolution CE-MRA and might be more useful than ToF-MRA (Lee YJ, 2015).

Two studies evaluated ultralow-dose Gd (2-3 mL) time-resolved MRA versus standard dose (0.1 mmol/kg) CE-MRA for the evaluation of supra-aortic arterial stenosis at 3T. These showed that image quality and diagnostic agreement for stenotic disease in ultralow dose time-resolved MRA scans using 2-3 mL were not inferior to standard dose CE-MRA (Bak, 2017; Lohan, 2009). However, Gd doses below 2 mL were considered limited in spatial resolution leading to a tendency of overestimating stenosis grade. Also for Gd doses as low as 0.047 mmol/kg MRA of the supra-aortic arteries can be performed at 3T, without compromising image quality, acquisition speed, or spatial resolution (Tomasian, 2008).
However, it should be noted that the imaging quality at local centres will depend on the local MRI physics expertise to implement non-CE MRA or ultra-low CE-MRA techniques.

*Abdominal vasculature, peripheral arteries, and vascular malformations*

For the abdominal aorta and pelvic vasculature only one study was identified that compared low dose (Takahashi, 2004) to standard dose CE MRA. Three studies have been published that evaluated hepatic vasculature using non-contrast MRA compared to CE sequences (Kumar, 2021; Luk, 2017; Puippe, 2012), indicating that CE-MRI is not superior in depicting hepatic anatomy.

Several comparative studies have been published that evaluated non-contrast MRA for the assessment of renal artery stenosis, in particular balances steady-state free precession MR angiography (b-SSFP MRA) has shown promise in diagnosing renal artery stenosis (Aydin, 2017; Braidy, 2012; Glockner, 2010; Khoo, 2011; Lal, 2021; Maki, 2007). Also the three- dimensional Fast Imaging Employing Steady-State Acquisition (3D-FIESTA) sequence has been compared to CE-MRA and digital subtraction angiography (Gaudiano, 2014), suggesting that also 3D FIESTA sequence could be a useful tool in evaluating RAS. Further studies are

needed to evaluate whether non-contrast MRA can truly replace CE-MRA to determine the presence of significant renal artery stenosis. Five studies were identified that evaluated non- contrast MRA for the evaluation of peripheral arterial occlusive disease. Although some studies were promising with regard to potential of non-contrast MRA techniques (Hodnett, 2011; Knobloch, 2021; Thierfelder, 2014), also concerns were expressed with regard to the rate of non-diagnostic vessel segments being considerably higher for non-contrast MRA than for CE-MRA (Diop, 2013; Schubert, 2016).

A specific indication of vascular imaging is the evaluation of vascular malformations. There is limited information in this disease group. One study evaluated a low dose CE protocol for diagnostic accuracy for treatment planning and follow-up but did not compare to standard dose MRI (Anzidei, 2011). For coil-embolized intra-cranial aneurysms it has been suggested that non-contrast ToF MRA can be used as a diagnostic alternative to CE ToF MRA (Behme, 2016).

*Heart*

With regards to cardiac imaging, various studies have been published that evaluated the possibilities of non-contrast imaging for various applications. This is of particular relevance in cardiac imaging considering that high-risk populations with chronic kidney disease often are referred for cardiac imaging due to concomitant cardiovascular disease as part of cardiorenal syndrome. Few studies have evaluated the possibilities of detecting myocardial fibrosis using non-Gd protocols (Graham-Brown, 2018) or with lowered Gd dose using higher-relaxivity contrast media such as gadobenate dimeglumine (Cheong, 2015; Galea, 2014). With regards to these studies, it can be concluded that the need of GBCA is of great relevance for the detection of myocardial disease as the distribution of the Gd chelate to the increased extracellular volume in the equilibrium phase is the pathophysiological marker of delayed enhancement imaging, which as this moment cannot be reliable replaced by existing non-contrast sequences.

Although low dose GBCA protocols can visualize myocardial fibrosis, standard dose protocols did result in overall better image quality and should be routinely preferred (Galea, 2014). One study evaluated non-contrast coronary MRA for the detection of significant coronary artery disease combined with subsequent Gd adenosine stress perfusion imaging of the heart (Heer, 2013), indicating that additional stress perfusion imaging with Gd substantially improved the diagnostic accuracy of detecting significant coronary artery disease. A specific group in which the application of reduced dose (Faggioni, 2012; Montalt-Tordera, 2021) and non-CE protocols (Chang, 2013; Elzayat, 2018; Isaak, 2021) have been evaluated are patients with congenital heart disease. For visualization of anatomy of the great vessels in congenital heart disease, non-contrast MRA protocols can be used as alternative to contrast-enhanced (CE) MRA protocols. One study described the potential of DL for the improvement of contrast in low-dose MRA studies in patients with congenital heart disease (Montalt- Tordera, 2021).

Gadolinium reduction strategies for musculoskeletal imaging

Four studies were identified that evaluated half dose imaging for musculoskeletal indications involving the assessment of synovitis or tenosynovitis (Schueller-Weidekamm, 2013), bone and soft-tissue disease in children (Colafati, 2018), bone and soft tissue tumours (Costelloe, 2011) and the evaluation of cartilage. These

studies indicate that half dose GBCA protocols may be used while maintaining image quality (Rehnitz, 2020), however the limited number of studies indicate the need for additional research on this topic.

Studies evaluating the added value of GBCAs to musculoskeletal imaging protocols were mainly focused on detecting synovitis in patients with osteoarthritis and in spinal imaging. Albeit non-CE sequences can visualize synovitis, these are limited with an underestimation for detecting synovitis in patients with osteoarthritis (Crema, 2013; de Vries, 2021; Eshed, 2015) and inflammatory arthritis (Hemke, 2013). A recent meta-analysis aimed at determining the correlation between knee synovitis assessed on non-CE and CE MRI with histology in patients with knee osteoarthritis found that CE MRI scores correlated best with inflammatory infiltrates of synovial tissue, while paucity of current evidence warrants further studies on non-contrast for detecting knee synovitis (Shakoor, 2020).

With regards to spinal imaging, only three studies have been published that evaluated the added diagnostic value of Gd to spinal imaging protocols. One study investigated the differentiation of epidural fibrosis from disc herniation (Passavanti, 2020), one the characterization of vertebral marrow infiltrative lesions (Zidan, 2014), and one debated the added value of post-Gd images in contrast to non-enhanced scans for diagnosis of spondylitis and its complications (Prasetyo, 2020).

Gadolinium reduction strategies for body imaging

*Prostate*

Several studies in the past few years have been performed that have investigated the performance of non-CE MRI of the prostate versus CE prostate MRI protocols. These studies have focused on the sensitivity and specificity of detecting prostate cancer using non- contrast imaging protocols (T2w + DWI [diffusion weighted imaging] sequences) compared to CE-imaging protocols (T2w + DWI + DCE [dynamic contrast enhanced imaging]). For the non-contrast imaging protocols the ranges for sensitivity and specificity of detecting clinically significant prostate cancer were respectively 63%-95% and 71-88%, compared to sensitivity and specificity ranging between 73-95% and 45-85% for protocols including Gd (Alabousi, 2019; Bass, 2021; Cuocolo, 2021; Knaapila, 2020; Kuhl, 2017; Liang, 2020; Niu, 2018; Park, 2021; Tamada, 2021). An overview of the main studies investigating the performance of non-contrast MRI of the prostate vs contrast MRI was recently summarized by Pecoraro (2021). For intra-procedural prostate imaging for identification of ablation zone extent, non-contrast T2*w-MRI in one study has shown to be comparable to CE T1w-MRI suggesting that this might be a method for repeated intra-procedural monitoring of the thermal ablation zone without the need for Gd (Sun, 2021). With regard to lowered Gd dose strategies for prostate cancer, only one small study in 17 patients was identified that evaluated whether administration of low doses of Gd for DCE MRI can be as effective as a standard dose in distinguishing prostate cancer from benign tissue (He, 2018).

*Liver*

Several studies have been performed that compared half-dose imaging with standard-dose imaging in liver MRI. Most studies focused on gadobenate dimeglumine which has high T1 relaxivity and can be used for both dynamic and delayed liver MRI. A blinded intra-individual study evaluating standard and low dose liver MRI

with gadobenate, found that albeit the standard dose yields greater relative enhancement, there is overall little improvement in subjective image quality (Kamali, 2020). Evaluation of enhancement patterns and characterization showed that half-dose and standard-dose liver MRI with gadopentetate dimeglumine found that 62 out of 64 lesions (97%) were identically characterized based on similar contrast enhancement compared to standard-dose gadodiamide (De Corato, 1999).

One study comparing half-dose gadobenate dimeglumine to standard dose gadopentetate dimeglumine showed that the half-dose imaging resulted in similar diagnostic information on dynamic imaging as well as the possibility of delayed imaging in the hepatobiliary phase (Schneider, 2003). Quarter-dose (0.025 mmol/kg) with gadobenate dimeglumine was compared retrospectively for image quality with half-dose imaging for abdominal MRI in patients at risk for nephrogenic systemic fibrosis, showing that the overall enhancement quality of the quarter dose was rated as good in all phases of enhancement, but was significantly lower than that for half-dose imaging (De Campos, 2011).

A recent meta-analysis study for surveillance MRI of hepatocellular carcinoma (HCC) using shortened MRI protocols (also referred to as abbreviated MRI) assessed the pooled sensitivity and specificity of contrast-enhanced hepatobiliary phase (HBP) abbreviated MRI (T2w, DWI, CE-T1w in HBP) and non-contrast abbreviated MRI (T2w, DWI, T1w dual-gradient echo imaging) (Kim, 2021). In this study there was a good overall diagnostic performance for detecting both any-stage HCC and early-stage HC, and the contrast-enhanced HBP abbreviated MRI showed a significantly higher sensitivity for detecting HCC than the non-contrast abbreviated MRI (87% vs. 82%) but had a significantly lower specificity (93% vs. 98%) ($p = 0.03$). The main limitation of the non-contrast abbreviated MRI is the relatively low lesion-to-liver contrast.

Also for liver metastases detection, non-contrast MRI protocols have been studied indicating that in particular DWI is an important sequence that improved mean specificity, positive predictive, negative predictive, and accuracy values for lesions either as small or greater than 1 cm (Colagrande, 2016). A comparative study in 175 patients with histologically confirmed 401 liver metastases and 73 benign liver lesions found no significant differences in sensitivity (range = 95.2-99.6%), specificity (range = 77.3-100%), positive predictive value (range = 92.9-100%) or negative predictive value (range = 87.5-95.7%) between the non- contrast MRI and the full MRI protocol with contrast (Hwang, 2019). These studies indicate that non-contrast liver MRI that includes DWI may serve as an alternative to contrast- enhanced MRI for detecting and characterizing liver metastases in patients with relatively high risk of liver metastases.

Finally, one study in patients with suspected possible choledocholithiasis evaluated the comparative performance of non-contrast MRI with half-Fourier acquisition single-shot turbo spin echo (HASTE) versus contrast-enhanced MRI/3D-magnetic resonance cholangiopancreatography (MRCP) (Kang, 2017). In this study the abbreviated non-contrast MRI with HASTE and full contrast-enhanced MRI/3D-MRCP resulted in high accuracy for choledocholithiasis (91.1-94.3% vs. 91.9-92.7%) and no differences in sensitivity or specificity were found, indicating that in patients with suspected choledocholithiasis, performance of non-contrast abdominal MRI with HASTE is similar to contrast-enhanced MRI with 3D-MRCP, offering potential for decreased scanning time and improved patient tolerability (Kang, 2017).

Other body imaging applications

Only few studies have been published that evaluate non-contrast MRI protocols for other body applications such as renal (Mawi, 2021), pancreatic (Lee, 2019), gastro-intestinal (Cattapan, 2019; Goshima, 2009; Kim SJ, 2019), and adnexal (Sahin, 2021) imaging. Albeit these studies are promising about the possibility of leaving out Gd-based sequences in MRI protocols without compromising diagnostic confidence, more studies are needed before specific recommendations on non-contrast MRI strategies for body imaging can be made.

Also for MRI studies with low dose strategies for renal renography and urography more evidence is needed (Bayrak, 2002).

Gadolinium reduction strategies for breast imaging

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is the most sensitive technique in breast imaging for the detection of breast cancer, however an increasing number of studies have investigated the potential of unenhanced or abbreviated MRI protocols without the need for GBCA in breast cancer imaging. In total seven studies were found that evaluated the application of non-contrast breast MRI protocols versus breast MRI protocols that include Gd based sequences. Although non-contrast sequences such as STIR and DWI have good specificity for the detection of breast cancer (Belli, 2016; Khalil, 2020; Telegrafo, 2015), reduced diagnostic performance for small lesions (<10 mm) limits the application of non-contrast breast MRI (Belli, 2016). Combining unenhanced MRI of the breast with additional breast tomosynthesis may improve the diagnostic accuracy of non- contrast breast MRI protocols (Girometti, 2020; Rizzo, 2021).

Some initial evaluation of the application of non-contrast breast MRI protocols has been performed in the context of evaluation of treatment response of neoadjuvant chemotherapy (Cavallo, 2019). One study evaluated high spectral and spatial resolution MRI (Medved, 2011) indicating the need for further research on new MRI sequences. In addition, protocols with reduced GBCA dose need further investigation. In the present literature search one study was identified that investigated a half dose Gd protocol for breast MRI. This study in 40 patients evaluated whether half dose gadobutrol (0.05 mmol/kg) was able to detect biopsy-proven breast cancers imaged at 3T using DCE MRI. All 49 breast cancers (of which approximately a quarter were smaller than 2 cm) were detectable using half dose gadobutrol on 3T MRI and did not differ in conspicuity scores (Melsaether, 2019).

**Recommendations**

*In general, it can be concluded that the evidence for non-CE imaging in applications where CE imaging is considered standard of care is still too scarce to be able to draw conclusions and for this reason in this section only remarks summarizing the body of literature are provided, and no active recommendations are formulated. Few comparative studies on reduced dose imaging have been performed from which the following can be recommended:*

1. Potential dose-reduction strategies for neuroimaging with gadolinium-based contrast agents

Findings of the LEADER-75 trial indicate that the dose of gadolinium-based contrast agents (gadobutrol) may be reduced to up to 75% of the standard dose (0.075 mmol/kg bodyweight, equivalent to 0.075 ml/kg bodyweight) in patients with suspected brain lesions.

The use of deep learning based methods for gadolinium dose reduction in patients suspected with brain metastasis is not recommended based on the current literature.

2. Potential dose-reduction strategies for cardiovascular imaging with gadolinium-based contrast agents

The use of standard dose imaging is recommended in patients with clinical indications for the administration of gadolinium-based contrast agents in in cardiac MRI.

Non-CE MRA techniques (e.g., time-of-flight MRA) and are widely available and can be used for accurate evaluation of stenosis grade of the supra-aortic vasculature.

Non-CE ECG-gated MRA sequences are widely available and recommended over (low- dose) CE MRA techniques for the evaluation of aortic dimensions.

3. Potential dose-reduction strategies for musculoskeletal imaging with gadolinium-based contrast agents

The use of standard dose imaging is recommended in patients with clinical indications for the administration of gadolinium based contrast agents in musculoskeletal imaging.

4. Potential dose-reduction strategies for abdominal imaging with gadolinium-based contrast agents

*Prostate*

There is increasing evidence that biparametric (T2w + DWI) protocols may be used as an alternative to multiparametric (T2w + DWI + DCE) protocols for the detection of prostate cancer (See also guideline on Prostate Cancer).

*Liver*

The use of standard dose imaging is recommended in patients with clinical indications for the administration of gadolinium based contrast agents in liver MRI.

5. Potential dose-reduction strategies for breast imaging with gadolinium-based contrast agents

The use of standard dose imaging is recommended in patients with clinical indications for the administration of gadolinium based contrast agents in breast MRI.

## Onderbouwing

## Onderbouwing

### Achtergrond

There is an increasing interest in the reduction of the use of gadolinium-based contrast agents (GBCAs) for clinical safety reasons, environmental aspects, logistics, and health care costs. Two main strategies for the reduction of GBCAs are imaging by using a lower dose (e.g., half-dose imaging or lower) than the standard used dose of gadolinium (Gd) of 0.1 mmol/kg body weight for contrast-enhanced (CE) MRI, as well as leaving out GBCA in MRI scan protocols to answer specific clinical questions. Leaving out GBCA involves specific clinical scenario's for various organ systems, and such approaches are to be discussed further within multi-disciplinary expert panels.

### Samenvatting literatuur

For this chapter it was decided not to perform a systematic literature analysis.

### Verantwoording

Laatst beoordeeld : 28-11-2022

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

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# GBCA en T1w hyperintensiteit in het brein

## Uitgangsvraag

Wat is de klinische relevantie van de GBCA-geïnduceerde T1w hyperintensiteit van de nucleus dentatus en de globus pallidus in de hersenen?

## Aanbeveling

Zorg voor een strikte indicatie voor met gadolinium versterkte MRI en gebruik door de EMA goedgekeurde GBCA bij alle patiënten om mogelijke gadolinium depositie te minimaliseren.

## Overwegingen

The following is a short overview of the current state of gadolinium retention in the brain and body. See also the Introduction to Safe Use of Gadolinium-Based Contrast Agents.

Increased SI due to Gd deposition
Two autopsy studies, both published in 2015, showed that the increased SI on $T_1$-weighted sequences ($T_1$w) in the dentate nucleus and globus pallidus was indeed due to the presence of retained Gd (Kanda, 2015; McDonald, 2015). The majority of the Gd was localized in the perivascular spaces (4), whereas a much smaller fraction crossed the blood-brain barrier and was situated in the neural interstitium and cellular organelles (Fingerhut, 2018; McDonald 2015; McDonald, 2017_1; McDonald, 2017_2).

Difference between linear and macrocyclic chelates
Subsequent studies confirmed progressive T1 SI increases after intravenous administration of linear GBCA (Errante, 2014; Kanda, 2015_1; Radbruch, 2015; Ramalho, 2015; Quattrocchi, 2015; Quattrocchi, 2015_1). The majority of the publications do not show dose-dependent changes in T1w SI after macrocyclic GBCA exposure (Cao, 2016; Kanda, 2015_1; Kromrey, 2017; Radbruch, 2017; Ramalho, 2015; Quattrocchi, 2015_1; Tibussek, 2017). Others report a weak T1w SI increase after administration of macrocyclic GBCA (Bjornerud, 2017; Kang, 2018; Rossi, 2017; Spelndiani, 2018; Stojanov, 2016;). A study of human brain tissue demonstrated measurable Gd after single dose intravenous administration of both linear and macrocyclic chelates (Murata, 2016). Significant less Gd retention was observed after macrocyclic chelate exposure, compared to linear chelate exposure (Murata, 2016).

These results led to a European Medicines Agency (EMA) directory regarding GBCA, stating to suspend the use of linear GBCA in order to prevent any risks that could potentially be associated with Gd brain deposition (EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans, 2019). Only the liver specific linear GBCA gadoxetate and gadobenate are allowed to be used in these situations where they meet a specific diagnostic need (EMA's final opinion confirms restrictions on use of linear GBCA in body scans, 2017).

Gd deposition in other tissues than brain.

Besides the brain and skin in patients with NSF, Gd retention has been reported in many other tissues including the bone, muscles, tendons, nerves, blood vessels and visceral organs (Gibby, 2004; Murata, 2016; Sanyal, 2011).

Pathophysiology of Gd deposition

Stability of Gd chelates is determined by their thermodynamic and kinetic stability. Thermodynamic stability of a chemical system means that this system is neither consuming nor releasing heat, i.e. thermal energy. In the absence of a change in thermal energy, the system is not undergoing a chemical reaction. Kinetic stability refers to the fact that a chemical reaction can occur at a certain speed. If a chemical system is kinetically stable, it means that reactions within this system occur very slowly. In general, macrocyclic GBCA have higher thermodynamic and kinetic stability constants and are therefore more stable than linear Gd chelates and therefore release less amount of $Gd^{3+}$ out of the chelate (McDonald, 2018). Very little is known about the fate of free $Gd^{3+}$ within the human body, and how biologically active and potentially toxic chemical forms of retained Gd in tissues are formed (McDonald, 2018). After intravenous injection in patients with normal kidney function, 73% to 99% of the dose is excreted within 24 hours after injection. Biodistribution data of GBCA suggest the presence of a longer lasting phase of residual excretion from other tissues, from which Gd is slowly eliminated (McDonald, 2018). The potential toxicities of this small pool of retained Gd are largely unknown (McDonald, 2018).

Clinical importance of Gd deposition

After hundred millions of Gd chelate administered doses, 139 patients with normal or minimally impaired kidney function reported effects that they associate with Gd exposure. The symptoms include chronic pain, fatigue, dermal changes, musculoskeletal disturbances, cognitive impairment, and visual impairment (Burke, 2016). An association between these symptoms and Gd chelate exposure has been postulated and the term “gadolinium deposition disease” has been proposed (Semelka, 2016). The Food and Drug Administration (FDA) could not find a causal relationship between Gd deposition and symptoms. If Gd deposition is associated with clinical harm, the harm is likely to be rare or occult for the vast majority of exposed patients (McDonald, 2018).

Future directions

Today, many question marks exist when it comes to the explanation of how Gd deposition occurs and what the clinical consequences, if any, are. In 2018, a research roadmap on Gd deposition was proposed, with the highest priorities to determine a) if Gd deposition adversely affects the function of human tissues, b) if deposition is causally associated with short- or long-term clinical manifestations of disease and c) if vulnerable populations are at greater risk for developing clinical disease (McDonald, 2018).

## Onderbouwing

## Achtergrond

In 2014, Kanda observed progressive unenhanced $T_1$-weighted ($T_1$w) signal intensity (SI) increases in the dentate nucleus and globus pallidus in patients who received at least 6 doses of Gadolinium (Gd) chelates (Kanda, 2014). This publication triggered a huge amount of research on this subject, which is still going on

today. Weekly, new publications arise, which make it impossible to give an up to date overview in this guideline. The broad outlines of gadolinium deposition will be discussed.

## Samenvatting literatuur

Not Applicable.

## Zoeken en selecteren

To answer our clinical question a systematic literature analysis was performed. This was an orientatational search, to examine the clinical relevance of the T1w hyperintensity of the nucleus dentatus and the globus pallidus.

**P** (Patient): Patients who have repeatedly received gadolinium-based contrast agents and have signs of gadolinium retention such as $T_1$w hyperintensity of the nucleus dentatus and the globus pallidus, but also gadolinium retention in the bones, liver and skin.
**I** (Intervention): Not applicable.
**C** (Comparison): Not applicable.
**O** (Outcomes): Signal intensity, signal increase, hyperintensity, hypersignal. Central torso and peripheral arm and leg pain. Distal arm and leg skin thickening. Rubbery subcutaneous tissues. Clouded mentation or brain fog.

Relevance of outcome measures
Signal intensity, signal increase, hyperintensity, hypersignal were considered critical outcomes and central torso, peripheral arm and leg pain, distal arm and leg skin thickening and rubbery subcutaneous tissues and clouded mentation or brain fog were considered important outcome measures.

Methods
The databases Medline (OVID), Embase and the Cochrane Library were searched from 1st of January 1996 to 11th of November 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS).

The literature search produced 722 hits. A total of 99 abstracts were selected. When the full texts were examined, none of them fulfilled the selection criteria. Based on this, it was concluded that no conclusions on the clinical aspect could be drawn. Based on the literature, the narrative review shown below was written by the guideline committee.

## Verantwoording

Laatst beoordeeld : 24-06-2020

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

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# Zwangerschap en lactatie

This module consists of two submodules.

## Verantwoording

Laatst beoordeeld :

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

# Veilig gebruik van contrastmiddelen tijdens de zwangerschap

## Uitgangsvraag

Wat is het veiligheidsprofiel van (jodiumhoudend en gadoliniumhoudend) contrastmiddel (CM) tijdens de zwangerschap voor moeder en kind?

## Aanbeveling

Onthoud geen zwangere patiënten van beeldvorming met jodiumhoudend contrastmiddel, wanneer dit medisch geïndiceerd is.

Wees terughoudend met gadoliniumhoudend contrastmiddel vanwege de potentiële risico's voor de foetus. Gebruik alleen contrastmiddelen wanneer de baten duidelijk groter zijn dan de risico's.

## Overwegingen

The use of diagnostic imaging with contrast media (CM) in pregnant patients has always been a topic of debate. It is known that administered CM pass the placenta and enter the foetal circulation in small amounts, but due to lack of hard data on the possible side effects for the foetus, it is difficult to give a solid advice to pregnant patients. Several reviews and papers found in literature use the results of limited data and recommendations of other guidelines (Lin, 2007; Little, 2020; Puac, 2017; Tremblay, 2012; Wang, 2012).

So far, different animal studies reported no congenital malformations with the use of iodine- based contrast media (ICM) (Morisetti, 1994). There are some theoretical concerns that free iodide can cause damage to the foetal thyroid gland (Webb, 2005).

With our search, only one comparative study was included for ICM. In this study no evidence was found that the administration of ICM caused congenital abnormalities or influenced the neonatal thyroid function (Rajaram, 2012). Three other non-comparative studies which were excluded from our search because of missing control groups, but were described in table 2.1, also did not report any congenital abnormalities (Atwell, 2008; Bourjelly, 2010; Kochi, 2012). Based on these findings we found no evidence that ICM cause congenital abnormalities. However, the evidence is uncertain due to the limited data and design of the few studies. Recently, a systematic review (Van Welie, 2021) found the same results regarding ICM with CT. They conducted a systematic review regarding ICM and their effect in pre-conceptional and post-conceptional women and their new-borns. They found five retrospective cohort studies and one case report regarding ICM in CT which reported on 525 neonates. Based on these five cohort studies, they estimated the overall proportion of (transient) neonatal thyroid dysfunction after CT at 0.0% (95% CI: 0.0–0.02% $I^2$=0%).

Due to these limited data, other guidelines were also consulted:

Guidelines from the Contrast Media Safety Committee (CMSC) of the European Society of Urogenital Radiology (ESUR) state that ICM may be given to the pregnant patient and that neonatal thyroid function should be checked during the first week (ESUR, 2018).

The Manual on Contrast Media from the American College of Radiology (ACR) recommends not withholding the use of ICM in pregnant or potentially pregnant patients when it is needed for diagnostic purposes (ACR, 2022).

Guidelines on ICM of the Royal Australian and New Zealand College of Radiologists (RANZCR) state that infants born to women who received ICM while pregnant should have testing for neonatal hypothyroidism (RANZCR, 2021).

Guidelines from The American College of Obstetricians and Gynaecologists (ACOG) state that ICM should only be used if absolutely required to obtain additional diagnostic information that will affect the care of the foetus or woman during the pregnancy (ACOG, 2017).

With gadolinium-based contrast agents (GBCA), animal studies have reported teratogenic effects only when administered in high and repeated doses (Chen, 2008; Novak, 1993; Okuda, 1999). Free gadolinium is toxic, and it is presumed that in high and repeated doses, gadolinium dissociates from its chelation agent. In humans, it is uncertain what the exact risk of gadolinium can be due to the unknown duration of exposure. When CM pass the placenta, it enters the foetal circulation and amniotic fluid. There, it re-enters the circulation due to swallowing of the amniotic fluid by the foetus. Therefore, the exact duration of foetal exposure to gadolinium is not known. The longer it remains in the amniotic fluid, the higher the risk of dissociation and exposure to free gadolinium.

No comparative studies were included with the use of GBCA. Two non-comparative studies shown in table 2.1, reported no adverse outcomes with the use of GBCA (De Santis, 2007; Spencer, 2000). In addition, Ray et al. (Ray 2016), performed a large retrospective study, evaluating the long-term safety of MRI exposure in pregnancy. They identified all births after 20 weeks of gestation in Ontario, Canada, from 2003 to 2015. Women exposed during first trimester of pregnancy to MRI and women exposed later in pregnancy were separately analysed. These were compared to women that were not exposed to MRI and had also no indication for MRI. For this reason, the study was excluded from the literature analysis.

Exposure to MRI during the first trimester of pregnancy (n=1.737), compared with non- exposure (n= 1.418.451), was not associated with increased risk of harm to the foetus. Stillbirths and neonatal deaths occurred among 7/397 (2%) MRI-exposed with gadolinium vs. 9844/1.418.451 (1%) unexposed pregnancies (adjusted RR, 3.70; 95% CI, 1.55 to 8.85) for an adjusted risk difference of 47.5 per 1000 pregnancies (95% CI, 9.7 to 138.2). They also found a significantly increased risk of a broad set of rheumatological, inflammatory, or infiltrative skin conditions. So far, this study is the only longitudinal cohort study with a significant sample size. However, limitations of this study for assessing the risk of gadolinium-based contrast agents are the unavailability of MRI indications of the exposed cohort, a bias towards linear GBCA, a low follow-up rate, no trimester subset analysis, and the lack of a comparable control group with indication for (non-contrast) MRI (Little, 2020; Lum, 2020).

In contrast, a very recent retrospective cohort study (published after our literature search) compared 782 pregnancies that were exposed to MRI with GBCA to 5,209 pregnancies that were exposed to MRI without GBCA out of a population of > 11 million Medicaid-covered pregnancies. The primary endpoint was

foetal/neonatal death, and the second endpoint was the infant neonatal intensive care unit admission rate. In both groups the percentage of foetal/neonatal death was 1,4%, with an adjusted relative risk of 0.73 (95% CI 0.34-1.55).

The percentage of infants with a neonatal intensive care unit admission was 7.7% in the GBCA and 8.8% in the non-GBCA group, with an adjusted relative risk of 1.03 (95% CI 0.76- 1.39). These results were considered reassuring for fatal and severe acute effects of GBCA administration during pregnancy, but subacute effects were not studied (Winterstein, 2022).

We also consulted other guidelines for their recommendations concerning GBCA: Guidelines from the CMSC of ESUR state when there is a strong indication for CE MRI, the smallest possible dose of a macrocyclic GBCA may be given to a pregnant female (ESUR, 2018; Webb, 2005 and 2013).

Guidelines from the Royal College of Radiology (RCR) state that GBCA should not be used during pregnancy unless the clinical condition of the patient makes their use absolutely necessary (RCR, 2019).

Guidelines from the ACR state that because it is unclear how GBCA will affect the foetus, these agents should be used with caution to pregnant or potentially pregnant patients. GBCA should only be used if their usage is considered critical and the potential benefits justify the potential unknown risk to the foetus (ACR, 2022).

Guidelines from the ACOG state that the use of GBCA with MRI should be limited. It may be used as a contrast agent in a pregnant woman only if it significantly improves diagnostic performance and is expected to improve foetal or maternal outcome (ACOG, 2021).

Guidelines from the Canadian Association of Radiologists on MRI do not recommend GBCA administration unless absolutely necessary (Jabehdar Maralani, 2022).

Based on our search and the advice from other guidelines, we made recommendations for the use of ICM and GBCA separately. Regarding our second clinical question, no recommendations could be made. None of studies regarding ICM made a distinction in gestational age. For GBCA, only a few studies focussed on the first trimester or women who did not know they were pregnant (Bird, 2019; De Santis, 2007). Their recommendations are like the overall recommendations. The guidelines which are mentioned earlier, also do not have recommendations for specific trimesters. The ACR has a separate document about imaging in potentially pregnant patients, but this document does not address the use of CM. Therefore, a recommendation about a specific trimester cannot be made and our recommendations will be for pregnancy in general.

**Recommendations**

*Our recommendation for the use of ICM is in line with the guidelines mentioned above. A discussion of the theoretical potential risks and benefits of the use of ICM should take place but a pregnant patient should not be denied a diagnostic test when it is needed. Because of the heel prick screening test, extra testing of the thyroid is not necessary.*

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| Do not withhold a pregnant patient from imaging with iodine-based contrast media when medically indicated. |

*Although no adverse outcomes were reported in the two studies mentioned in table 2.1, our recommendation regarding the use of GBCA is in line with other guidelines. The recommendation is based on the study of Ray et al (2016) and the potential teratogenic risks found in animal data.*

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| Be cautious with gadolinium-based contrast agents due to potential risks to the foetus. Only use contrast agents when the benefits clearly outweigh the possible risks. |

## Onderbouwing

### Achtergrond

Little is known about the safety of the use of contrast media (CM) in pregnant patients, both for the mother and the unborn child. Not only the caregiver but also the patients themselves have many questions about the safety of CM. The confusion about this safety can lead to avoidance of a potential crucial diagnostic test. Therefore, an updated search is highly needed.

### Conclusies / Summary of Findings

*Iodine-based contrast media*

| | |
|---|---|
| **Very low GRADE** | Iodine-based contrast medium administration may have little to no effect on neonatal thyroid function when compared with no iodinated contrast medium administration in pregnant patients, but the evidence is very uncertain.<br><br>*Sources: Rajaram, 2012* |

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|---|---|
| **No GRADE** | No evidence was found regarding the effect of iodine-based contrast medium administration on congenital defects other than thyroid function when compared with no iodine-based contrast medium administration in pregnant patients. |

*Gadolinium-based contrast agents*

| | |
|---|---|
| **No GRADE** | No evidence was found regarding the effects of gadolinium-based contrast agent administration on congenital defects when compared with no contrast medium administration, or a different type of contrast medium administration in pregnant patients. |

### Samenvatting literatuur

Description of studies

*Iodine-based contrast media*
Rajaram, 2012 performed a retrospective review of 115 pregnant patients investigated for suspected pulmonary embolism. The patient cohort consisted of two groups: Group A consisted of 73 pregnant females who received iodinated contrast agent for CT-pulmonary angiography (CTPA), and Group B (control group) consisted of 42 pregnant females who were investigated by perfusion imaging only. For group A, a maximum dose of 100 ml of non-ionic iodinated low-molecular-weight agent containing 300 mg/ml iopromide was used as a standard contrast agent. The gestational age at the time of contrast administration was in Group A (median 28 weeks, range 12-40) and Group B (median 29 weeks, range 7-38, p- 0.30). The results of the neonatal thyroid function tests for the babies of the mothers in Groups A and B were compared. The blood samples for TSH levels were obtained from new- borns by heel puncture test at the age of 5–8 days.

*Gadolinium-based contrast media*
No studies with a control group were found. Descriptive studies without control group can be found in Table 2.1.

Results

*Iodine-based contrast media*
Rajaram (2012) reported that no significant difference was found in neonatal TSH values between the two groups (p=0.67). The average TSH value for group A, exposure to iodinated contrast agent, was 1.1 mIU/ml. The average TSH value for group B, no exposure to iodinated contrast agent, was 1.07 mIU/ml.

*Gadonium-based contrast media*

**Table 5.1: Brief description of studies that have the same patient population and intervention group as the search question, but no control group**

| Study name | Patient population and number | Type of contrast medium | Results | Other remarks |
|---|---|---|---|---|
| Iodine-based contrast media | | | | |

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|---|---|---|---|---|
| Atwell, 2008 | N=21<br>pregnant patients who underwent CT with iodinated IV contrast material between February 2000 and October 2006. Mean maternal age at the time of CT was 29 years (range, 19–41 years). Mean gestational age (based on last menstrual period) at the time of CT was 23 weeks<br>(range, 8–37 weeks). Neonatal patients were born at a mean of 38 weeks of gestation (range, 24–41 weeks of gestation) | CT with iodinated IV contrast material (type was not further specified) | For all neonatal patients, serum TSH levels were normal. Mean<br>serum TSH was 9.7 µIU/mL (range, 2.2–28.8 µIU/mL).<br>No maternal patient reported thyroid problems in her child | Author's conclusion: Based on neonatal TSH measurements in a small number of patients, we found no ill effect of iodinated contrast agents on neonatal thyroid function after in utero exposure.<br><br>Retrospective observational study. |

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| Bourjelly, 2010 | N=344<br>All pregnant women who underwent multidetector pulmonary computed tomographic angiography because they were suspected of having pulmonary embolism between 2004 and 2008 and new-borns resulting from the index pregnancy were included.<br>Mean gestational age at the time of administration of the contrast material was 27.8<br>weeks 6 7.4. | Iohexol.<br>The mean dose of total iodine administered was 45 000 mg/L 6 7321. | All new-borns had a normal T 4 level at birth; only one new-born had a transiently abnormal TSH level at birth, which normalized at day 6 of life.<br>This new-born was born to a mother who had many drug exposures during pregnancy. | Author's conclusion:<br>A single, high-dose in utero exposure to water-soluble, low-osmolar, iodinated intravenous products, such as iohexol, is unlikely to have a clinically important effect on thyroid function at birth.<br><br>Retrospective observational study. |

| | | | | |
|---|---|---|---|---|
| Kochi, 2012 | N=61 (64 neonates) pregnant women receiving iodinated contrast during a CT scan procedure, and their neonates.<br>The mean age of mothers in this group was 27.6 years at the time that they underwent a CT scan procedure. The mean GA at the time of the procedure was 25.6 weeks. The earliest GA was 8 weeks and the latest was 37 weeks. The mean GA at delivery was 37.5 weeks. Eight women had hypothyroidism.<br><br>A control group of 6 pregnant patients that received an CT scan without iodinated contrast was included. *(Since the control group contained <10 patients, this study was excluded from the literature analysis.)* | Iodinated contrast<br><br>The mean amount of non-ionic radioiodine contrast material used was 103.5 mL of Ultravist 300, which is approximately equal to 30 g of iodine. The range was between 21 and 46 g of iodine. | The TSH and T4 levels for all neonates, except one in this group, were within the reference range of 0.5 to 6.0 KIU/mL for TSH and 7 to 14 Kg/dL for T4. One neonate had a T4 level of less than 6 Kg/dL and a normal TSH level. This patient was a preterm infant being born at the 25th week of gestational age who also developed respiratory distress syndrome and sepsis. | Author's conclusion: This study concludes that there is no significant adverse clinical risk of thyroid function abnormalities to the foetus after IV iodinated contrast material to their mothers.<br><br>Retrospective observational study. |
| Gadolinium-based contrast agents | | | | |

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|---|---|---|---|---|
| De Santis, 2007 | N=26<br>Pregnant women exposed to gadopentetate dimeglumine in the periconceptional and first trimester period who had undergone an MRI owing to other clinical indications. Age: 31 ± 4 years The mean menstrual age at exposure was 29.78 days and 24/26 exposures were in the postconceptional period. | Gadopentetate dimeglumine | Two pregnancies, exposed at 15 and 18 days of menstrual age were complicated by low-birth- weight infants (LBW) but without any neonatal complications.<br>One congenital anomaly at birth in a baby that had two haemangiomas born at 38 weeks to a woman exposed at 31 days of menstrual age through an MRI for a pituitary adenoma. | Author's conclusion: In this prospective cohort study, we found no maternal or neonatal complications and only one congenital anomaly at birth.<br><br>Prospective observational study. |

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| Spencer, 2000 | N=11<br>Women with symptomatic hydronephrosis during pregnancy<br>(1) clinical features of loin pain in pregnancy as assessed by an obstetrician and urologist; (2) ipsilateral dilatation of the renal pelvis shown by routine abdominal sonography; and<br>(3) informed consent of the patient.<br>19–34 weeks of gestation.<br>Patient age not reported. | IV bolus of 0.1 mmol/kg of gadopentatate dimeglumine | There were no adverse obstetric or infant outcomes. | Author's conclusion: MR excretory urography is a promising technique which affords equivalent functional and additional anatomical information to isotope renography.<br><br>Prospective study. |

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|---|---|---|---|---|
| Ray, 2016 | N= 397 exposed to gadolinium MRI and N=1 418 451 not exposed. Women with first trimester exposure to MRI. | Gadolinium-enhanced MRI during first trimester | "There were 7 stillbirths or neonatal deaths (17.6 per 1000) following gadolinium-enhanced MRI exposure (cohort 2) vs 9844 events (6.9 per 1000) in nonexposed women, an adjusted RR of 3.70 (95% CI, 1.55-8.85) and an adjusted risk difference of 47.5 per 1000 (95% CI, 9.7-138.2)" | Author's conclusion: "Exposure to gadolinium enhanced MRI at any gestation was not associated with a greater risk of congenital anomalies. Although the NSF-like outcome was extremely rare, gadolinium- enhanced MRI was associated with an adjusted HR of 1.36 for any rheumatological, inflammatory or infiltrative skin condition up to age 4 years, and an adjusted RR of 3.70 for stillbirth or neonatal death, albeit with just 7 events in the gadolinium MRI group." |
| | | | | |

Level of evidence of the literature

*Iodine-based contrast media*
The level of evidence regarding the outcome measure thyroid function started as GRADE low due to the observational nature of the included study was downgraded by one level to very low due to the small number of included patients (imprecision).

*Gadolinium-based contrast agents*
No studies with a control group were found. Therefore, no evidence tables, risk of bias assessment and quality assessment were performed for the studies mentioned in Table 2.1.

## Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: What are the effects of contrast media during pregnancy for mother and child regarding safety?

**P** (Patients): Pregnant women with indication for examination with contrast media.

**I** (Intervention): Contrast media administration (iodine-based or gadolinium-based).
**C** (Comparison): No contrast media administration or different contrast media administration.
**O** (Outcomes): Foetal: congenital malformation (e.g., thyroid), maternal: adverse events.

**Relevant outcome measures**
The guideline working group considered congenital malformations as a critical outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the presence of a congenital malformation as a minimal clinically (patient) important difference. Because of the severity of the outcome any statistically significant difference was considered as a clinically important difference between groups.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from January 1st, 2000, until January 26th, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 507 hits. Studies were selected based on the following criteria:

- Original clinical studies or systematic reviews of original clinical studies; both randomized and observational studies were eligible
- Patient population consisted of pregnant patients
- The safety profile of contrast media administration regarding foetal congenital malformations was compared between women who received contrast media versus those who received no contrast media or a different contrast medium
- Iodine-based contrast media (ICM) or gadolinium-based contrast agent (GBCA)

Initially, thirty-one studies were selected based on title and abstract screening. After reading the full text, thirty studies were excluded (see Table of excluded studies in 'Appendices to modules') and one study was included.

Results
One study (Rajaram, 2012) about iodine-based contrast media was included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables and the assessment of the risk of bias is summarized in the risk of bias tables
('Appendices to modules'). Six studies were found that had the correct patient population and intervention group, but no control group, or no ICM or GBCA. These studies are briefly described in Table 2.1. Since the studies do not answer the search question, no quality of evidence analysis or evidence tables have been made for them.

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

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# Veilig gebruik van contrastmiddelen tijdens de lactatie

## Uitgangsvraag

Wat is het veiligheidsprofiel van (jodiumhoudend en gadoliniumhoudend) contrastmiddel (CM) tijdens de lactatieperiode voor moeder en kind?

## Aanbeveling

Vanwege de beperkte excretie van CM in de moedermelk, is de werkgroep van mening dat het veilig is om borstvoeding te continueren na toediening van CM.

Als de patiënte de borstvoeding zelf wenst te onderbreken (gezamenlijke besluitvorming met de arts), dan is een tijdsperiode van 24 uur voldoende.

## Overwegingen

Data from studies evaluating the safety of the use of contrast media (CM) in the lactation period are very limited (Böhm, 2020). Our search did not find any studies regarding lactation. Therefore, a recommendation based on findings of comparative studies cannot be made. However, we can make a recommendation based on the pharmacokinetics of CM and recommendations of other guidelines. Several reviews found in literature use pharmacokinetics and the results of limited animal studies. Most of their recommendations are also found in other guidelines (Cova, 2014; Lin, 2007; Puac, 2017; Tremblay, 2012; Wang, 2012).

When assessing the risk of CM in the lactation period, information of the excretion of these CM into breast milk and the absorption from the gastrointestinal tract of the new-born is needed. Iodine-based contrast media (ICM) and gadolinium-based contrast agents (GBCA) are water-soluble and therefore excreted in small amounts in breast milk, found in limited animal studies (Bourrinet, 1995; Lorusso, 1994; Okazaki, 1996). Human studies have stated the same, but numbers of patients are also very limited. These studies mention the excretion and later absorption of CM by the newborn, which are also mentioned in the guidelines from The American College of Radiology (ACR) and The American College of Obstetricians and Gynecologists (ACOG). They state that for ICM less than 1% of the administered maternal dose is excreted into breast milk in the first 24 hours. The absorption from the gastrointestinal tract in the newborn is 1%, making the systemic dose less than 0,01%. For GBCA, 0,04% of the administered maternal dose is excreted into breast milk. Combined with the 1% absorption, the systemic dose is less than 0,0004% (Kubik-Huch, 2007; Nielsen, 1987; Schmiedl, 1990; Tremblay, 2012; Wang, 2012; Webb 2005). Due to the small dose of CM in breast milk, these studies state that it is safe for both mother and newborn to continue breastfeeding after receiving CM. The ACR also states that the decision should be left up to the mother herself. If discontinuation of breastfeeding is wanted, 12-24 hours is enough (ACR, 2022).

The Contrast Media Safety Committee (CMSC) of the European Society of Urogenital Radiology (ESUR) guideline states that breastfeeding may be continued normally with ICM and GBCA (ESUR, 2018; Webb 2005 and 2013).

The guideline regarding GBCA of the Royal College of Radiology (RCR) states that, while no special precaution or cessation of breastfeeding is required, the continuation or cessation of breastfeeding for 24 hours should be at the discretion of the lactating mother in consultation with the clinician (RCR, 2019).

The guideline regarding ICM of the Royal Australian and New Zealand College of Radiologists (RANZCR) states that cessation of breastfeeding or expression and discarding of breast milk after ICM administration are not required (RANZCR, 2018).

The guideline on MRI in the obstetric patient of the Society of Obstetricians and Gynaecologists of Canada states that it is safe to continue breastfeeding after receiving GBCA (Patenaude, 2014).

**Recommendations**

*Our recommendation is in line with other guidelines and the few available data. Due to the limited amount of excretion of CM in breast milk, breastfeeding can be continued without interruption when imaging with CM is needed. If women wish to discontinue, a discontinuation of 24 hours should be enough.*

| |
|---|
| Due to the limited amount of excretion into breast milk, the guideline development group believes it is safe to continue breastfeeding after administration of contrast media. |

| |
|---|
| If patients wish to discontinue breastfeeding (shared decision making), a discontinuation of 24 hours is sufficient. |

## Onderbouwing

### Achtergrond

The same questions about the use of contrast media (CM) in pregnancy arise in the puerperium, especially when breastfeeding. Questions arise from mothers, who are administered CM, whether these substances are safe for the new-born during the lactation period. This chapter is intended to provide recommendations regarding this topic.

### Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: What are the effects of contrast media during the lactation period for mother and new-born regarding safety?

**P** (Patients): Lactating women with indication for examination with contrast media.
**I** (Intervention): Contrast media administration.
**C** (Comparison): No contrast media administration or administration of a different contrast medium.
**O** (Outcomes): Neonatal adverse effects: gastrointestinal effects, hypersensitivity reactions, thyroid effects, maternal effects: percentage of contrast medium in breast milk, transition into breast milk.

Relevant outcome measures
The guideline working group considered neonatal adverse effects (hypersensitivity reactions, gastrointestinal

effects, thyroid effects) of CM in breast milk as crucial outcome measures for decision making; and maternal effects (the percentage of contrast medium in breast milk) as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the presence of any neonatal adverse effect as a minimal clinically (patient) important difference. Because of the severity of the outcome any statistically significant difference was considered as a clinically important difference between groups.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from January 1st, 2000, until January 26th, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 507 hits.

Studies were selected based on the following criteria:

- Original clinical studies or systematic reviews of original clinical studies; both randomized and observational studies were eligible.
- Patient population consisted of patients who were breastfeeding.
- The safety profile of contrast media administration regarding neonates' effects and percentage of contrast medium in breast milk was compared between women who received contrast media versus those who received no contrast media or a different contrast medium.

Thirty-one studies were initially selected based on title and abstract screening. After reading the full text, all studies were excluded (see Table of excluded studies in 'Appendices to modules').

Results
No studies were included in the analysis of the literature, and therefore no systematic literature analysis was performed.

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

## Referenties

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# Zeldzame ziekten

This module consists of four submodules.

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

# Veilig gebruik van contrastmiddelen bij patiënten met multipel myeloom

## Uitgangsvraag

Welke preventiestrategieën zijn effectief om contrastmiddel-geassocieerde acute nierschade (CA-AKI) bij patiënten met multipel myeloom te voorkomen?

## Aanbeveling

Neem altijd de algemene principes voor preventie van acute nierschade in acht, die al werden gepubliceerd in hoofdstuk 2. PC-AKI:

- Optimale nefrologische zorg dient het primaire doel te zijn bij alle patiënten met chronische nierziekten, met specifieke aandacht voor hydratiestatus en medicatiegebruik.
- Streef naar klinische euvolemie, gebruik normaal saline of Ringer's lactaat, voorafgaand aan een onderzoek met intravasculair jodiumhoudend CM, ongeacht de eGFR waarde.
- Beschouw patiënten met een eGFR <30 ml/min/1,73m$^2$ tot een hoogrisico-groep voor CA-AKI.
- Consulteer een internist/nefroloog bij patiënten met een eGFR <30 ml/min/1,73m$^2$.

Bepaal bij elke patiënt met een multipel myeloom of toediening van jodiumhoudend CM noodzakelijk is, of dat alteratieve beeldvorming mogelijk is:

- Pas dezelfde voorzorgsmaatregelen toe om CM-geassocieerde acute nierschade (CA- AKI) te voorkomen bij patiënten met multipel myeloom als bij patiënten zonder deze ziekte, wanneer er geen extra risicofactoren zijn, geassocieerd met multipel myeloom, voor het ontwikkelen van acute nierinsufficiëntie.
- Voor (euvolemische) patiënten met een eGFR <30 ml/min/1,73m$^2$ waarbij intravasculair jodiumhoudend CM toegediend zal worden, prehydreer de patiënt met 3ml/kg/u NaHCO3 1,4% gedurende 1 uur (of 250ml in totaal) voor toediening van het CM.

Bij geselecteerde patiënten met extra risicofactoren voor het ontwikkelen van acute nierinsufficiëntie (bijv. hypercalciëmie, lichte keten nefropathie, amyloïdose) is voorafgaand overleg tussen hematoloog en radioloog of cardioloog nodig om een betrouwbare inschatting te maken van de voordelen en de risico's. Hierbij moet worden bepaald of er een absolute indicatie is voor de toediening van jodiumhoudend CM en of preventieve maatregelen in dat geval noodzakelijk zijn.

## Overwegingen

The discussion whether multiple myeloma per se is an independent risk factor for contrast- associated acute kidney injury (CA-AKI) goes back as far as the early 1990s (McCarthy, 1992; Pahade, 2011). CA-AKI is synonymous with post-contrast acute kidney injury (PC-AKI) used in part 1 and part 2 of this guideline, but CA-AKI is currently more frequently used than PC-AKI for this condition.

Pros and cons of the intervention and quality of the evidence

The systematic review belonging to the ESUR guideline (Stacul, 2018) and the retrospective cohort study by Crowley (2018) were excluded from the literature analysis because of limited study quality and the lack of a control group without multiple myeloma. Results will be discussed descriptively.

The systematic review for the ESUR guideline (Stacul, 2018) reported on CA-AKI in patients with multiple myeloma and monoclonal gammopathies. CA-AKI was defined as cases in which kidney injury could not be explained by other causes than contrast medium administration. Twelve cohort studies and one case control study were included, the majority uncontrolled and of limited quality (Newcastle-Ottawa scores of 5-6 out of a scale until 9). Reference values of a control group without multiple myeloma were not reported. High osmolality contrast media were used in eleven studies, whereas low osmolality contrast media were used in the remaining two studies. Many important variables were not reported such as the multiple myeloma description (subtype, stage, disease load), baseline serum creatinine and calcium concentration, or number of examinations per patient. In addition, existing kidney injury after one month and the need for dialysis were not reported. A total of 642 patients and 824 iodine-based CM administrations were studied.

Crowley et al. (Crowley, 2018) reported on CA-AKI in patients with multiple myeloma. The study was retrospective and carried out in a university hospital in Ireland using a medical record database to retrieve information. CA-AKI was defined as a > 25% increase or a rise of more than 44.2 mmol/L (0.5 mg/dL) in serum creatinine level above baseline level after receiving IV contrast material within three days of administration of contrast media. In contrast to the ESUR guideline (Stacul, 2018), characteristics of the multiple myeloma patients (demographics, subtype, stage, disease load), baseline serum creatinine and calcium concentration were described. The study was uncontrolled and of limited study quality. The type of contrast medium used was not described, patients on dialysis were excluded, and information on infection, hydration status or use of nephrotoxic drugs was not available. The study, however, did report on existing kidney failure after one month. In total 94 patients with multiple myeloma, including 165 procedures with contrast media, were available for analysis.

The incidence of CA-AKI will be described separately because of the different definitions of CA-AKI, different inclusion criteria and the inclusion of monoclonal gammopathies patients besides multiple myeloma patients (Stacul, 2018).

*CA-AKI*
The reported CA-AKI case incidence in the ESUR guideline (Stacul, 2018) was 12/824 procedures (1.6%) among 642 patients with multiple myeloma or monoclonal gammopathies. The two studies using low osmolality contrast media comprised 210 CT examinations in 76 patients, in whom CA-AKI was observed in 4/210 cases (1.9%).
The reported CA-AKI incidence by Crowley (2018) was 17/165 procedures (10%) among 94 patients with multiple myeloma. The severity of the CA-AKI was not described. The 94 patients received on average two procedures with iodinated contrast (2.1±1.5). In 47% of procedures (77 procedures) baseline creatinine was elevated and 4% of procedures (6 procedures) had elevated baseline calcium. In the whole group, there was no significant difference between the serum creatinine concentration before and after the contrast- enhanced procedure (p=0.08).

*Existing acute kidney injury after 1 month*
The cohort study by Crowley (2018) reported 10/17 CA-AKI cases (59%) demonstrated a normalised serum creatinine within one month of the procedure. This means that kidney function was not restored to normal in 7/17 (41%) of cases. However, the severity of renal function loss was not quantified. Moreover, it is not clear to which extent these 7 cases represented the same individuals who showed an elevated serum creatinine at baseline.

From evidence to decision
About 50% of patients with multiple myeloma may develop acute or chronic renal failure in the course of the disease. Major causes of renal failure are light chain cast nephropathy and hypercalcemia. Other causes of renal failure in multiple myeloma are e.g., amyloidosis, nephrotoxic drugs, or hyperuricemia. The literature does not provide clear evidence that multiple myeloma per se predisposes to a higher risk for development of CA-AKI independent of the renal function. The available literature is, however, of limited quality. In general, administration of contrast media in patients with multiple myeloma seems to be safe. In view of the enhanced overall risk for renal failure, however, an alternative imaging technique that does not require iodine-containing CM should always be considered. When administration of iodine-containing CM is deemed necessary, special attention in these patients is required to provide optimal nephrology care as outlined in Safe Use of Contrast Media part 1. In particular, to avoid dehydration and nephrotoxic stimuli and medications, and to provide intravenous prehydration in patients with eGFR <30 ml/min/1.73m$^2$.
In selected patients with additional risk factors such as light chain cast nephropathy, hypercalcemia, or amyloidosis, close consultation between the haematologist and the imaging physician is recommended to assess the benefit-risk ratio of ICM administration and whether preventive measures or an alternative imaging technique are warranted.

Evidence from other contrast media is very scarce. In line with iodine-based contrast media, the use of gadolinium-based contrast agents does not seem to negatively affect renal function in myeloma patients (Hillengass, 2015).

Costs
Although keeping a low threshold for application of volume expansion protocols may seem a safe strategy of prevention of CA-AKI, such protocols present a logistic and financial burden to the hospital system (Kooiman, 2013). Particularly the longer pre- and post-hydration schedules will require admission of patients that could otherwise have their CT performed in an outpatient setting. To admit all patients at increased risk for AKI in day-hospital wards for intravenous volume expansion is expensive, and the volume expansion itself may lead to complications as well. Cost arguments differ for in-hospital patients if it does not lead to an extended hospital stay.

**Recommendations**

*In general, administration of contrast media in patients with multiple myeloma seems to be safe. These patients, however, have an enhanced overall risk for renal failure as a result of several concomitant risk factors that might be present.*

Always consider the general principles of prevention of acute kidney injury that were outlined in Safe Use of Contrast Media, Part 1:

- Optimal nephrology care should be the primary goal in all chronic kidney disease patients, with attention to hydration status and medication use.
- Aim for clinical euvolemia, using normal saline or Ringer's lactate, before administration of intravascular iodine-based contrast media, regardless of eGFR.
- Consider patients with an eGFR <30 ml/min/1.73m$^2$ at risk for CA-AKI.
- Consult a nephrologist/internist for patients with an eGFR <30 ml/min/1.73m$^2$.

Determine in each patient with multiple myeloma whether administration of iodine-based contrast media is indicated or if an alternative imaging technique is possible:

- Apply the same precautions to prevent contrast-associated acute kidney injury (CA- AKI) in patients with multiple myeloma as in subjects without this disease, if there are no additional risk factors associated with multiple myeloma for development of acute renal insufficiency.
- For (euvolemic) patients with an eGFR <30 ml/min/1,73m$^2$ undergoing intravascular administration of iodine-based contrast media prehydrate with 3ml/kg/h NaHCO3 1.4% for 1h (or a total of 250ml) pre-CM administration.

*In a minority of patients with multiple myeloma, several precipitating factors for acute kidney insufficiency might be present, necessitating consultation between the imaging physician and the treating haematologist.*

In selected patients with additional risk factors associated with multiple myeloma for development of acute renal insufficiency (e.g., hypercalcemia, light chain cast nephropathy, amyloidosis), close consultation between the haematologist and imaging physician is needed to ensure an optimal risk-benefit balance, including whether administration of contrast media is warranted and if preventive measures are needed.

## Onderbouwing

### Achtergrond

Multiple myeloma (MM) is a plasma cell neoplasm accounting for 1.0-1.8% of all cancers. It represents the second most common haematological malignancy with an incidence in Europe of 4.5-6.0/100,000/year (Dimopoulos, 2021; Sprangers, 2018). It has been suggested that patients with multiple myeloma are more prone to develop contrast-associated acute kidney injury (CA-AKI) (synonymous with post-contrast acute kidney injury (PC-AKI)) than would be expected based on their renal function (LeBlanc, 2002). The question arises whether multiple myeloma represents a risk factor for CA-AKI, necessitating additional preventive measurements irrespective of the renal function.

### Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: What is the risk of

contrast-associated acute kidney injury (CA-AKI), existing kidney injury after one month or the need for dialysis in multiple myeloma patients following administration of contrast media compared to patients without multiple myeloma?

**P** (Patients): Patients with multiple myeloma.
**I** (Intervention): Administration of contrast media.
**C** (Comparison): Patients without multiple myeloma.
**O** (Outcomes): Contrast-associated acute kidney injury (CA-AKI), existing acute kidney injury after 1 month, need for dialysis.

Relevant outcome measures
The guideline development group considered existing kidney injury after 1 month and the need for dialysis as critical outcome measures for decision making; and CA-AKI as important outcome measures for decision making.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until February 17th, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 124 hits. Studies were selected based on the following criteria: (1) patients with multiple myeloma (2) examination with contrast media (3) comparison to patients without multiple myeloma (if possible) and (4) one of the previously described outcomes. Fifteen studies were initially selected based on title and abstract screening. After reading the full text, fifteen studies were excluded (see Table of excluded studies in 'Appendices to modules') and no studies were included. One systematic review by Stacul (2018) and one retrospective cohort study by Crowley (2018) were found. These papers could not be included in the literature analysis because of the limited quality of the included studies and the lack of a comparable control group without multiple myeloma or reference values. These two publications, however, will be described in more detail in the justifications, as they represent the best available evidence.

**Results**
No studies were included in the literature analysis, and therefore, no systematic literature analysis was performed.

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

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# Veilig gebruik van contrastmiddelen bij patiënten met een feochromocytoom of paraganglioom

## Uitgangsvraag

Wat voor strategie wordt aanbevolen om contrastmiddel veilig toe te dienen bij patiënten met een feochromocytoom of paraganglioom?

Deze klinische vraag bevat de volgende subvraag:

- Hoe zou intra-arterieel en intraveneus contrast moeten worden toegediend bij patiënten met een feochromocytoom of paraganglioom?

## Aanbeveling

Profylactische therapie met een adrenerge α-receptorblokker (± adrenerge ß-receptorblokker) is niet geïndiceerd bij intraveneuze toediening van jodiumhoudend CM bij patiënten met een feochromocytoom of paraganglioom.

Profylactische therapie met een adrenerge α-receptorblokker (± adrenerge ß-receptorblokker) is niet geïndiceerd bij intra-arteriële toediening van jodiumhoudend CM bij patiënten met een feochromocytoom of paraganglioom.

Gadoliniumhoudend CM en CM voor echografisch onderzoek kunnen veilig worden gebruikt bij patiënten met een feochromocytoom of paraganglioom.

## Overwegingen

Pheochromocytomas and paragangliomas (PPGL) are rare neuroendocrine tumours derived from chromaffin tissue of the adrenal medulla and the extra-adrenal sympathetic paraganglia in the thorax and abdomen, respectively (Nölting, 2022). The annual incidence of PPGL in The Netherlands is approximately 100 new cases, with about 80 cases presenting as a pheochromocytoma (Berends, 2018). PPGL have the capacity to produce and release excessive amounts of catecholamines into the circulation. Uncontrolled release of catecholamines can be provoked by several mechanical and pharmacological stimuli (e.g., intubation, tumour manipulation, various drugs), which may result in acute blood pressure elevation, tachyarrhythmias and life-threatening cardiovascular events (so-called pheochromocytoma crisis). To prevent these complications, pre-treatment with antihypertensive agents is usually started prior to surgery. Administration of a-adrenergic receptor blockers is recommended as treatment of first choice. Tachycardia is treated with ß-adrenergic receptor blockers but should only be given to a patient who is already receiving an α-adrenergic receptor blocker for several days. Neglect of this basic treatment principle may result in a pheochromocytoma crisis with serious cardiovascular complications due to unopposed stimulation of α-adrenergic receptors with ensuing severe peripheral vasoconstriction (Sibal, 2006).

There is only one small non-randomised prospective study (n=22) comparing the effect of treatment with adrenoreceptor blocking agents prior to intravenous administration of low- osmolar CT contrast in patients

with a PPGL. In this study, 11 patients received pre- treatment with an α- and/or ß-adrenergic receptor blocker, whereas 11 patients did not receive this premedication (Baid, 2009). Adverse events were not observed in any of these patients. In addition, plasma catecholamine levels within and between groups were not significantly different before and after intravenous administration of contrast medium. The absence of a change in plasma catecholamine levels after intravenous administration of nonionic contrast media in patients with PPGL was also demonstrated in a previous study (Mukherjee, 1997). Moreover, no adverse events were recorded in a retrospective study of 25 patients with PPGL receiving nonionic IV iodine-based contrast media without premedication (Bessell-Browne, 2007).

Based on these observations, intravenous administration of low-osmolar CT contrast is safe in patients with a PPGL without the need of prophylactic treatment with an α- or ß- adrenergic receptor blocker.

Patient series on intra-arterial administration of CT contrast are not available. A survey among six centres of expertise (i.e., five centres in the Netherlands plus the National Institute of Health, Bethesda, USA) demonstrated that five out of six centres would not start prophylactic treatment with an α- or ß-adrenergic receptor blocker in case of intra-arterial administration of CT contrast (personal communication).

There are no data on safety issues when using gadolinium-based or ultrasound contrast agents in PPGL patients.

**Recommendations**

*There are no randomised studies evaluating the efficacy of prophylactic treatment in case of intravenous administration of radiocontrast medium in patients with PPGL. Limited data do not suggest that administration of radiocontrast medium provokes an uncontrolled release of catecholamines into the circulation or is associated with adverse events in patients with PPGL. We therefore consider intravenous administration of low-osmolar CT contrast to be safe in patients with a PPGL without the need of prophylactic treatment with an α- or ß- adrenergic receptor blocker.*

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| Prophylactic treatment with an α-adrenergic receptor blocker (± ß-adrenergic receptor blocker) is not indicated before intravenous administration of iodine-based contrast media in patients with pheochromocytoma or paraganglioma. |

*There are no randomised studies or case series evaluating the efficacy of prophylactic treatment in case of intra-arterial administration of radiocontrast medium in patients with PPGL. This suggests that this route of administration is safe, which is also in agreement with the outcome of our brief survey among several centres of expertise. We therefore consider intra-arterial administration of low-osmolar CT contrast to be safe in patients with a PPGL without the need of prophylactic treatment with an α- or ß-adrenergic receptor blocker.*

| |
|---|
| Prophylactic treatment with an α-adrenergic receptor blocker (± ß-adrenergic receptor blocker) is not indicated before intra-arterial administration of iodine-based contrast media in patients with pheochromocytoma or paraganglioma. |

*There are no data on safety issues when using gadolinium-based or ultrasound contrast agents for imaging in PPGL patients.*

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| Gadolinium-based contrast agents and ultrasound contrast agents may be safely used in patients with pheochromocytoma or paraganglioma. |

## Onderbouwing

### Achtergrond

It has been suggested in the past that intravascular administration of contrast media in PPGL patients may provoke a hypertensive crisis (Eisenhofer, 2007). This raises the question whether treatment with α-adrenergic receptor blockers prior to administration of radiocontrast agents is required to prevent such a crisis.

### Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: Which strategies are effective in preventing a hypertensive crisis in patients with pheochromocytoma?

**P** (Patients): Patients with pheochromocytoma or sympathetic paraganglioma and an indication for examination with contrast media.
**I** (Intervention): Contrast administration with a-blockers, b-blockers, calcium channel blockers.
**C** (Comparison): Contrast administration without additional preventive strategy.
**O** (Outcomes): Cardiovascular complications, hypertensive crisis.

Relevant outcome measures
The guideline development group considered cardiovascular complications as a critical outcome measure for decision making; and hypertensive crisis as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 22-2-2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 125 hits. Studies were selected based on the following criteria five studies were initially selected based on title and abstract screening. After reading the full text, five studies were excluded (see Table of excluded studies in 'Appendices to modules'), and no studies were included.

Results
No studies were included in the analysis of the literature, and therefore, no systematic literature analysis was performed.

### Verantwoording

Laatst beoordeeld : 28-11-2022

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

## Referenties

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# Veilig gebruik van contrastmiddelen bij patiënten met Myasthenia Gravis

## Uitgangsvraag

Wat is de rol van contrastmiddelen (CM) bij patiënten met exacerbaties van myasthenia gravis na CM-toediening?

## Aanbeveling

Onthoud patiënten met myasthenia gravis niet van beeldvorming met CM omdat het risico op exacerbatie door CM erg laag is.

## Overwegingen

Mehrizi, et al. (2014) found that in 81 CTs with contrast and in 23 MRIs with contrast no presence or absence of ADRs was reported. The study was not included in the systematic literature analysis because of severe methodological limitations. There were no cases of increasing myasthenic weakness. No immediate increased risk was noted about gadolinium- based contrast agents with regards to worsening myasthenic symptoms. There is no immediately increased risk for exacerbation of myasthenic weakness with the use of modern low-osmolar ICM. No weakness was reported in patients who received IV GBCA. The authors concluded that there is no immediately increased risk for exacerbation of myasthenic weakness with the use of modern low-osmolar radiologic contrast agents.

All three studies had significant methodological limitations. There seems to be only a very minimal risk of a myasthenic crisis following the administration of iodine-based contrast media. This does not justify withholding ICM for diagnostic studies.

There is no data on any risk after administration of other contrast media, such as gadolinium-based or ultrasound contrast agents.

### Recommendations

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| Do not withhold contrast media to patients with myasthenia gravis, as the risk of a contrast media-induced myasthenic exacerbation is very low. |

## Onderbouwing

## Achtergrond

It is unclear whether contrast media can cause exacerbation of myasthenia gravis (MG) symptomatology for which MG patients should be warned or premedicated.

## Conclusies / Summary of Findings

| | |
|---|---|
| **Very low GRADE** | The evidence is very uncertain about the effect of contrast media on exacerbations in patients with myasthenia gravis.<br><br>*Sources: Rath, 2017, Somashekar, 2013* |

| | |
|---|---|
| **No GRADE** | No literature was found regarding the risk of neurological exacerbations of myasthenia in MG patients with using contrast medium in comparison to MG patients with different contrast medium administration or contrast medium administration without preventive strategy. |

**Samenvatting literatuur**

Description of studies

Rath, et al. (2017) performed a retrospective cohort study, where the rate of acute adverse events as well as delayed clinical worsening up to 30 days was analysed. In 73 patients with confirmed MG who underwent contrast-enhanced CT studies with the administration of low osmolality iodinated contrast agents (ICAs) and compared to 52 patients who underwent unenhanced CT studies. Limitations of this study were (1) selection bias for the enhanced and unenhanced CT scans (2) the relatively low patient numbers (3) the retrospective nature of the investigation which entails the possibility that some adverse events might have been missed in some patients as they had to rely on electronic medical records. To minimize this effect, investigators only included patients with a sufficient clinical information available. Finally, the exact characteristics of the used contrast agents could not be extracted retrospectively from the available data in all patients; therefore, they could not compare the potential side effects of different ICAs with each other.

In a retrospective cohort study by Somashekar, et al. (2013), a computed tomography (CT) was performed in 267 paediatric and adult patients with clinically confirmed MG between January 1, 1995, and December 31, 2011. CT was performed without intravenous administration of contrast material in 155 patients and with intravenous administration of low-osmolality contrast material in 112 patients. Electronic medical records were searched to identify myasthenia gravis–related symptoms (i.e., bulbar, ocular, respiratory, or extremity weakness) before (≤14 days) and after (≤45 days) each CT examination. All contrast-enhanced CT examinations were performed with one of a variety of low-osmolality contrast media. A variety of baseline characteristics and risk factors were collected for each patient, with attention to (a) the disease status of the patient's myasthenia gravis immediately before CT (i.e. stable, worsening, or improving), (b) history of thymectomy, and (c) acute or chronic cardiac and/ or pulmonary and/or neuromuscular disease not related to myasthenia gravis. Limitations of this study were (1) retrospective nature of the study (2) selection bias between the control group and the experimental group, (3) some adverse events may not have been captured and (4) unable to determine the volume or type of contrast material administered in a large fraction of patients owing to incomplete documentation.

Results

Rath, et al. (2017) found that 9 of 73 patients (12.3%) experienced a delayed worsening of myasthenic

symptoms, i.e., they reached the primary endpoint of progressing by at least one grade in the MGFA classification within 30 days. The medical files of all 9 patients were reviewed and it was concluded that in none of these 9 patients the exacerbation was causally related to the contrast medium. The rate was higher in comparison with the control group of patients receiving CT scans without ICM (3.8%), but the difference did not reach statistical significance. In a subgroup analysis, six of these nine patients (8.2% of all patients) developed a severe deterioration, i.e., a myasthenic crisis, or died in comparison with none in the control group. The mean time to worsening within 30 days did not differ significantly between the two study groups and was 11.1 days for patients with contrast-enhanced CT studies and 13 days in the control group.

Somashekar, et al. (2013) demonstrated that intravenous administration of a low osmolality iodine-based contrast medium (ICM) is associated with a significant increase in the frequency of disease-related symptoms within 1 day of administration (P=0.01) compared to no intravenous administration of contrast media. The exacerbation frequency is 5.7% above the baseline rate observed in unenhanced CT control group (6.3%- 0.6%). This implies that intravenous low-osmolality ICM is associated with a 5%–6% frequency of acute symptom exacerbation in patients with myasthenia gravis. No difference in symptom frequency at 2–7 days or 8–45 days after CT were detected, indicating that the association between intravenous low-osmolality ICM and symptom progression is a relatively acute association. The contrast-enhanced CT group was associated with a significant reduction in time to disease-related symptom progression following CT (median time to onset of symptom progression, 2.5 days with contrast-enhanced CT vs 14.0 days with unenhanced CT; P=0.05). Acute exacerbations were primarily respiratory (five patients with new-onset dyspnoea: four in contrast-enhanced CT group and one in unenhanced CT group, two patients with progressive dyspnoea: both in the contrast-enhanced CT group), and one patient with progressive weakness: in contrast-enhanced CT group.

Summary of study's conclusions

Rath, et al. (2017) concluded that ICM administration for CT studies in MG patients should not be withheld if indicated, but patients particularly those with concomitant acute diseases should be carefully monitored for exacerbation of symptoms.

Somashekar, et al. (2013) concluded that intravenous administration of low-osmolality contrast media is significantly associated with exacerbation of myasthenia gravis–related symptoms. Exacerbations most commonly manifest as new or progressive acute respiratory compromise. Yet, review of the medical files showed no causative effect of the contrast medium.

Level of evidence of the literature

The level of evidence regarding the outcome measure ***neurological exacerbations of myasthenia*** started on a low GRADE due to the observational nature of the included studies and was downgraded by one level to a very low GRADE because of number of included patients.

## Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

**P** (Patients): Patients with myasthenia gravis and an indication for examination with contrast media.
**I** (Intervention): Contrast medium administration with or without preventive strategy (prednisolone, acetylcholine-reuptake inhibitors).
**C** (Comparison): No contrast medium administration, different contrast medium administration; contrast medium administration without preventive strategy.
**O** (Outcomes): Neurological exacerbations of myasthenia.

**Relevant outcome measures**

The guideline development group considered neurological exacerbations of myasthenia as a critical outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from January 1st, 2000, until March 4th, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 84 hits. Studies were selected based on the following criteria: (1) patients with myasthenia gravis (2) indication for examination with contrast media (3) comparison to patients with no contrast medium administration, different contrast medium administration or contrast medium administration without preventive strategy and (4) the previously described outcome. Eleven studies were initially selected based on title and abstract screening. After reading the full text, nine studies were excluded (see Table of excluded studies in 'Appendices to modules'), and two studies were included. One study, mentioned in the justifications, was not included in our literature analysis (Mehrizi,2014). It did not meet our PICO criteria and was excluded because of the wrong population, including children, and the absence of a comparison group.

Results
Two studies (Rath, 2017; Somashekar, 2013) were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

## Referenties

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# Veilig gebruik van contrastmiddelen bij patiënten met Mastocytose

## Uitgangsvraag

Welke strategieën zijn effectief om hypersensitiviteitsreacties en anafylactische shock te voorkomen bij patiënten met systemische mastocytose na contrastmiddel(CM)-toediening?

## Aanbeveling

Onthoud patiënten met systemische mastocytose niet van beeldvorming met een jodiumhoudend of gadoliniumhoudend CM.

Aanbevelingen bij toedienen van contrastmiddelen bij patiënten met systemische mastocytose:

- Continueer antiallergische onderhoudsmedicatie (v.b. H1/H2-antihistamine)
- Wees alert om te reageren op een mogelijke hypersensitiviteitsreactie
- Observeer de patiënt ≥ 30 min met behoud van intraveneuze toegang
- Na een allergische reactie, verwijs indien nodig naar een allergoloog

## Overwegingen

Pros and cons of the intervention and quality of the evidence
Clonal mast cell disorders are characterized by the uncontrolled expansion and accumulation of mast cells in one or multiple organs. The term cutaneous mastocytosis is reserved for patients with aberrant mast cell infiltration limited to the skin. Involvement of bone marrow with or without other affected organs (including skin, gastrointestinal tract) leads to the diagnosis of systemic mastocytosis (SM). Mast cells are proinflammatory innate immune cells that can be activated by various stimuli, including allergens, microbes, viruses, and toxins. Upon activation, mast cells degranulate and thereby release various proinflammatory substances and lipid mediators, including tryptase and histamine. These mast cell-derived mediators lead to allergic symptoms and, in case of severe mast cell degranulation, may induce anaphylactic shock. Since patients with mastocytosis have increased numbers of mast cells and the activation threshold for these mast cells is lower due to mutations in their constitutively expressed KIT receptor, patients with systemic mastocytosis are at increased risk of anaphylaxis.

Besides the previously mentioned stimuli, there are several drugs and substances with an (theoretically) increased risk for mast cell degranulation. Potential elicitors are NSAIDs, general anaesthesia, and iodine-based contrast media (ICM); gadolinium-based contrast agents (GBCA) do not impose an increased (theoretical) risk. Hence, they were avoided as much as possible in systemic mastocytosis, although this practice is gradually changing. If given, these drugs and substances are administered cautiously and mostly with concomitant use of anti-allergic premedication, consisting of antihistamines and corticosteroids. However, since the actual clinical risk has seldom been studied systematically under real world conditions due to practical and ethical concerns, it is to date unclear how often and relevant drug-induced mast cell degranulation are for this patient category. Moreover, recent studies suggested that the risk of drug-induced

anaphylaxis has been overestimated. For example, a double-blind placebo-controlled challenge with acetylsalicylic acid in patients with mastocytosis (n=50) elicited a mild hypersensitivity reaction in only one subject (Hermans, 2018).

One narrative review reported on the management of invasive procedures in mastocytosis including administration of contrast media (Hermans, 2017). The review did not represent a systematic literature search and did not describe the search methodology and could therefore not be included in the literature analysis. However, Hermans (2017) provided an overview of the risk of adverse reactions including anaphylaxis in patients with mastocytosis after contrast media administration. In addition, the review reported on premedication.

Hermans (2017) reported on four cohort studies among 457 adults with systemic mastocytosis who received contrast media (Brockow, 2008; González de Olano, 2007; Gülen, 2016; Hermans, 2016). Serious radiocontrast-related hypersensitivity was reported in 3/457 patients (0.65%), including development of anaphylaxis in one patient (0.22%) (Hermans, 2017). The number of cases in which premedication was used was not described. The number of serious adverse reactions in the general population to intravenous contrast administration was reported 0.5 to 3% for mild immediate reactions and 0.01 to 0.04% for serious adverse events (Andreucci, 2014; Thong, 2011). Hermans (2017) concludes there is no rationale for avoidance of contrast media in patients with mastocytosis, although some patients can be at increased risk for developing anaphylaxis. This applies particularly to patients with previous mast cell mediator-related symptoms during procedure, previous history of anaphylaxis (regardless of trigger), atopic background, use of b-blockers, ACE inhibitors or NSAIDs or severe mastocyte infiltration of the skin. Not only drugs, but also physical stimuli (temperature change, exercise, strong odours, pressure, friction) and emotional stress could potentially evoke non-IgE-mediated mechanisms that might cause mast cell degranulation. It is recommended to consider a patient-tailored risk assessment to assess which patients are indicated for premedication (Hermans, 2017).

A similar systematic literature search on the safety of contrast media was conducted in the soon to be published Dutch FMS guideline on mastocytosis 2022, which also did not yield any comparative studies on this subject. In that guideline it is cautiously suggested that iodinated contrast media can be safely applied in the majority of mastocytosis patients (Quality of evidence N/A; Hermans 2017). As a result, it is recommended to develop a personalized management plan for each mastocytosis patient after the diagnosis is made (FMS richtlijn Mastocytose, 2022).

Finally, Schwaab, et al. (2022) recently reported a retrospective analysis of 162 patients with indolent or advanced mastocytosis. Four of them (2.5%) reported a previous hypersensitivity reaction to iodinated contrast media. Hundred forty-eight (91%) of those patients underwent additional imaging, including 80 CT in 56 patients and 252 MRI in 127 patients. In 35 (24%) patients both types of scans were performed. Imaging without application of contrast media was obtained in 14 (9%) patients (CT, n=7; MRI, n=17). Daily anti-mediator therapy, including H1/H2 antihistamines and/or low dose prednisolone was continued. Additional prophylactic premedication (H1- and H2 antihistamine and 50mg methylprednisolone 30-60 minutes prior to the scan) was applied prior to 6 scans; 326/332 (98%) of the scans were performed without additional premedication. No contrast-mediated hypersensitivity reactions occurred. The authors conclude that in the

absence of a previous contrast mediated hypersensitivity reaction, use of premedication prior to contrast enhanced imaging may be dispensable. Systemic mastocytosis patients represent a heterogeneous group of patients and as a result, values and preferences of both patients and physicians may vary widely. Whether or not to use premedication may cause anxiety or medicalization depending on the patient's perspective.
For patients that have been diagnosed with systemic mastocytosis for a long time and have had uneventful iodinated contrast media administration under premedication (without premedication-related side effects), the adaptation of this protocol may cause unwarranted anxiety. In contrast, a newly diagnosed mastocytosis patient with no history of anaphylaxis may experience premedication as unnecessary medicalization, particularly if the patient has experienced side effects with these drugs in the past.

Costs
The direct costs of applying anti-allergic premedication with prednisolone and/or antihistamines are negligible, as the price of these drugs is very low. Therefore, one should consider the potential indirect costs of additional logistic procedures, as well as the potential adverse effects. These are low for antihistamines (mostly drowsiness) but occur for prednisolone, particularly in weakened patients and upon repetitive exposure.
Side effects include:

- Risk of glucose dysregulation, particularly in patients with diabetes.
- Risk of osteoporosis, particularly upon repetitive exposure.
- Risk of immune suppression, particularly upon repetitive exposure.
- Risk of temporary cognitive effects such as delirium, particularly in weakened patients. In severe cases, these side-effects may lead to hospitalization.

On the other hand, omitting premedication may potentially increase the risk of anaphylaxis, which will probably result in hospitalization with the associated costs. Therefore, premedication should be recommended in high-risk patients, i.e., patients with previous mast cell mediator-related symptoms during medical procedures, history of anaphylaxis (regardless of trigger), atopic background, use of b-blockers, ACE inhibitors or NSAIDs or severe mastocyte infiltration of the skin.

Acceptability, feasibility, and implementation
Based on the abovementioned arguments, it is not feasible to make one standard recommendation for the entire group of systemic mastocytosis patients. Recommending premedication in all patients is not indicated as it would lead to unnecessary anxiety, medicalization, side effects and associated costs in a selection of patients. Complete discourage of premedication however may lead to increased risk of anaphylaxis in a selection of patients. The treating physician should perform this risk assessment.

**Recommendations**
*It is important not to withhold iodinated contrast media from patients with systemic mastocytosis in case administration is necessary for optimal imaging. Despite the probably slightly increased risk of anaphylaxis (0.22% in mastocytosis versus the reported 0.01 to 0.04% for serious adverse events in the general population), the benefits of the imaging procedure should outweigh this small risk.*

Do not withhold iodine-based contrast media or gadolinium-based contrast agents in patients with systemic mastocytosis.

*Since there is no convincing evidence that use of anti-allergic premedication is beneficial for systemic mastocytosis patients prior to iodinated contrast administration, there is in general no need to apply this. However, systemic mastocytosis remains a heterogeneous disease with varying clinical symptoms and patients may suffer from comorbidities that should be considered. As a result, it is recommended that their treating physician with knowledge of both the disease and this specific patient should assess whether premedication should be employed. Patient with previous anaphylaxis, extensive skin involvement, use of ß-blockers, ACE inhibitors or NSAIDs may be at increased risk of developing anaphylaxis and additional premedication could be considered. Many mastocytosis patients already use H1- antihistamines (up to 4x the recommended daily dose) as part of their regular medication and these drugs should be continued. Preferably, the decision is shared by the patient and the physician and made timely before the patient needs iodine-based contrast media. The recommendation should be clearly reported in the electronic patient records. Comparable to other patient populations, it is possible that systemic mastocytosis patients develop an IgE-mediated allergy for a specific type of contrast. Therefore, in case a hypersensitivity reaction occurs, patients should be referred to a drug allergy specialist for further analysis.*

Recommendation for administration of contrast media in patients with systemic mastocytosis:

- Continue maintenance anti- allergic medication (e.g., H1-/H2-antihistamines).
- Be vigilant to react to a possible hypersensitivity reaction.
- Observe the patient ≥ 30 min with IV in place.
- In case of an allergic reaction, refer to a drug allergy specialist.

## Onderbouwing

### Achtergrond

It is unclear whether iodinated contrast media can cause hypersensitivity reactions in patients with systemic mastocytosis and whether prevention strategies should be employed.

### Samenvatting literatuur

No studies could be included in the literature analysis. Therefore, no systematic literature analysis could be performed.

### Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: what is the efficacy of a preventive strategy with prednisone and/or antihistamines next to contrast administration compared to contrast administration without additional preventive strategy on the risk of developing anaphylactic shock, (drug) hypersensitivity reaction, anaphylactic allergic reaction in patients with systemic mastocytosis?

**P** (Patients): Patients with systemic mastocytosis and indication for examination with iodine-based contrast media.
**I** (Intervention): Contrast media administration with prednisone and/or antihistamine premedication.
**C** (Comparison): Contrast media administration without additional premedication or other preventive strategies.
**O** (Outcomes): Anaphylactic shock, (drug) hypersensitivity reaction, anaphylaxis, allergic reaction.

**Relevant outcome measures**

The guideline development group considered anaphylactic shock and anaphylaxis as critical outcome measures for decision making; and (drug) hypersensitivity reaction and allergic reaction as an important outcome measure for decision making. A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until March 5th, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in twenty-one hits. Studies were selected based on the following criteria: (1) patients with systemic mastocytosis and an indication for examination with iodinated contrast media (2) comparing the adverse effects of contrast administration with prednisone and/or antihistamines administration with contrast administration without additional preventive strategy and (3) investigating one of the previously described outcomes. Five studies were initially selected based on title and abstract screening. After reading the full text, no studies could be included.

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

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# Jodiumhoudend CM en Diabetes Mellitus (DM)

## Uitgangsvraag

Dient metformine te worden gestaakt voorafgaand aan intravasculaire jodiumhoudend contrastmiddel(CM)-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 CM intravasculair wordt toegediend.

Staak metformine bij alle patiënten met een eGFR <30ml/min/1,73m$^2$ bij wie intravasculair jodiumhoudend CM 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/1.73$m^2$), 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/1.73$m^2$ and starting metformin in patients with an eGFR between 30 to 44 ml/min/1.73$m^2$ 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.
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$^2$.

## Onderbouwing

### Achtergrond

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 / Summary of Findings

| | |
|---|---|
| | 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.<br><br>*(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

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

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# Preventie van contrastmiddel-geïnduceerde encefalopathie (CIE)

## Uitgangsvraag

Wat zijn strategieën om contrastmiddel-geïnduceerde encefalopathie (CIE) te voorkomen?

## Aanbeveling

Zorgmedewerkers zouden alert moeten zijn op het voorkomen van contrastmiddel-geïnduceerde encefalopathie (CIE) na toediening van een jodiumhoudend contrastmiddel (CM).

Adequate preventiestrategieën zijn niet in detail onderzocht. Het algemene advies voor de klinische praktijk:

1. Minimaliseer de hoeveelheid toegediend jodiumhoudend CM zoveel mogelijk tijdens endovasculaire interventies
2. Overweeg om patiënten met een ernstige verminderde nierfunctie (eGFR <30 ml/min/1.73m2) te hydrateren voordat jodiumhoudend CM wordt toegediend (zie protocol in Hoofdstuk 2. PC-AKI).
3. Monitor patiënten de eerste 6 uur na endovasculaire interventies voor neurologische symptomen en consulteer laagdrempelig een neuroloog bij ontstaan van neurologische symptomen.
4. Behandel, afhankelijk van de klinische symptomen van CIE, met anti-epileptische medicatie, corticosteroïden, intraveneuze hydratatie en/of mannitol.

## Overwegingen

Contrast-induced encephalopathy is a complication of iodine-based contrast media (ICM) affecting the central nervous system. Usually, CIE is associated with intra-arterial administration of ICM during cardiac catheterization (Spina, 2017) or neuro-interventional procedures (Quintas-Neves, 2020), however, it can also occur after intravenous administration (Hinsenveld, 2017; Law, 2012). It can be challenging to distinguish CIE from thromboembolic stroke after endovascular procedures, of which the latter is a far more common complication. Patients may therefore be misdiagnosed and not adequately treated.

Symptoms arise within 24h after administration of ICM and include an altered mental status, focal neurological deficits, seizures, aphasia, and transient cortical blindness (Allison, 2021; Chu, 2020; Dunkley, 2021). It has been hypothesized that ICM disrupts the blood-brain barrier due to its hyperosmolarity, resulting in oedema and neurologic dysfunction (Chu, 2020; Dunkley, 2021; Matsubara, 2017; Kariyanna, 2020). Diagnosis is often a combination of both clinical and radiologic findings. Imaging typically shows cortical and subcortical contrast enhancement on CT and vasogenic oedema on MRI. Dual Energy CT can differentiate haemorrhage from contrast staining (Chu, 2020).

Risk factors include haemodialysis, hypertension, previous stroke, diabetes mellites, kidney disease, large volumes of ICM and previous adverse reactions (Allison, 2021; Matsubara, 2017). Renal dysfunction impairs clearance of contrast medium, and may result in more severe CIE, while previous stroke may already have disrupted blood-brain barriers (Chu, 2020; Matsubara, 2017; Zhang, 2020).

In most cases of CIE, spontaneously resolution of symptoms has been reported in several days with supportive care, although patients with permanent symptoms have also been described (Leong, 2012; Niimi, 2008; Shinoda, 2004; Zhao, 2019). Median time to recovery was reported to be around 30 hours (Kocabay, 2014).

The systematic research did not identify any comparative studies, but some potential preventative strategies have been proposed in the literature. Some advice to use low- osmolar ICM instead of iso- or high osmolar ICM, but in the recent years CIE has still been observed with low osmolar ICM and no comparative case-control studies have been performed (Kariyanna, 2020; Quintas-Neves, 2020, Spina, 2020). It has been reported that in most patients with CIE more than 100 ml ICM was administered. Limiting the amount of ICM administration or diluting ICM could be beneficial (Kariyanna, 2020).

One of the risk factors for developing CIE is renal dysfunction (Chu, 2020; Matsubara, 2017). It has been advocated that haemodialysis in patients with renal dysfunction might be beneficial in case of CIE, but no comparative studies have been performed (Matsubara, 2017). In the general population good hydration is generally advised around ICM administration (see protocol in Chapter 2. PC-AKI), although it is uncertain if this can avoid CIE. Another risk factor is hypertension. Hypertension itself can also induce a hypertensive encephalopathy. Whether lowering blood pressure before ICM administration decreases the risk of CIE is unknown.

In case of CIE, corticosteroid treatment has been advocated (Allison, 2021). Corticosteroid treatment may be used as preventative treatment in patients who previously have developed CIE or as a treatment to resolve the neurological symptoms during CIE. Animal studies showed that premedication with low molecular weight dextran and corticosteroids reduced the neurotoxic effects of contrast media, due to prevention of blood cell aggregation and decreased osmotic permeability of the blood brain barrier (Kariyanna, 2020). However, no studies in humans exist to date to support these findings.

A general recommendation is to closely observe patients directly after endovascular interventions, as most cases of CIE occur within the first few hours after intervention (Kocabay, 2014).

**Recommendations**

*No comparative studies were identified to provide evidence-based strategies to avoid CIE. The recommendations below are based on expert opinions.*

Health care providers should be aware of the existence of Contrast-Induced Encephalopathy (CIE) following iodine-based contrast media administration.

Adequate prevention strategies have not been investigated in detail. General advice for clinical practice:

1. Minimize the amount of iodine-based contrast media as much as possible during endovascular interventions.
2. Consider to hydrate patients with severe renal dysfunction (eGFR <30 ml/min/1.73m$^2$) receiving iodine-based contrast media (see protocol in Chapter 2. PC-AKI).
3. Closely monitor patients the first six hours after endovascular interventions for neurological symptoms and consult a neurologist immediately in case of neurological symptoms.
4. Depending on the clinical symptoms of contrast-induced encephalopathy, treatment with antiepileptic drugs, corticosteroids, intravenous hydration, and/or mannitol may be recommended.

## Onderbouwing

### Achtergrond

Contrast-induced encephalopathy (CIE) is a rare complication of the use of iodine-based contrast media (ICM), affecting the central nervous system. It has been associated with the administration of large volumes of ICM during endovascular interventions. This module aims to report on the optimal management of this complication as well as on strategies to prevent CIE.

### Samenvatting literatuur

No studies were included in the analysis of the literature. Therefore, no systematic literature analysis could be performed.

### Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: Which strategies are effective for prevention of Contrast-Induced Encephalopathy (CIE)?

**P** (Patients): Adult (>18 years) patients, with an indication for examination with intravenous or ICM administration.
**I** (Intervention): Prevention strategy - ICM administration with one type or volume of contrast medium.
**C** (Comparison): No prevention strategy (care as usual) - ICM administration with another type or volume of ICM.
**O** (Outcome): Contrast-induced encephalopathy, severity of CIE, neurotoxicity.

Relevant outcome measures
The guideline development group considered contrast-induced encephalopathy as a critical outcome measure for decision making; and severity of CIE, neurotoxicity as important outcome measures for decision making.

The working group defined the outcome measure contrast induced encephalopathy as follows: a complication of intravenous or intra-arterial contrast administration resulting in a clinical deterioration, not caused by stroke, seizures, and other metabolic abnormalities, with oedematous changes on brain imaging, usually accompanied with contrast staining (Chu, 2020; Quintas-Neves, 2020).

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until July 20th, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 419 hits. Studies were selected based on the following criteria: the description of contrast induced encephalopathy or neurotoxicity after administration of contrast media and the comparison of one preventive strategy to another strategy. Nineteen studies were initially selected based on title and abstract screening. After reading the full text, no studies were included.

Results
No studies were included in the analysis of the literature. Therefore, no systematic literature analysis could be performed.

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

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# Preventie van jodium-geïnduceerde hyperthyroïdie (IIHT) na het gebruik van jodiumhoudend contrastmiddel

## Uitgangsvraag

Wat zijn strategieën voor de preventie van jodium-geïnduceerde schildklierdysfunctie (IIHT) na het gebruik var jodiumhoudend contrastmiddel (CM) bij:

- Patiënten met een geschiedenis van hart- en vaatziekten
- Patiënten van meer dan 65 jaar oud
- Patiënten met een geschiedenis van schildklier problemen (struma, hyperthyroïdie, hypothyroïdie)

## Aanbeveling

Meet de schildklierfunctie niet routinematig voor toediening van jodiumhoudend CM.

Overweeg meting van de schildklierfunctie bij patiënten met een verhoogd risico op het ontwikkelen van jodium-geïnduceerde hyperthyreoïdie, vooral bij personen ouder dan 65 jaar en patiënten met ernstige cardiovasculaire morbiditeit.

Overweeg een profylactische behandeling in geselecteerde patiënten met subklinische hyperthyreoïdie, die jodiumhoudend CM ontvangen, bijvoorbeeld patiënten ouder dan 65 jaar oud of met ernstige cardiovasculaire morbiditeit.

Start profylactische therapie één dag voor CM-toediening en continueer 14 dagen met thiamazol (30 mg eenmaal per dag) en voeg indien nodig kaliumperchloraat toe (500mg tweemaal per dag).

Vermijd isotopen-beeldvorming van de schildklier en/of behandeling met radioactief jodium tot 4-8 weken na injectie van jodiumhoudend CM. Of geef geen jodiumhoudend CM 4-8 weken voor een geplande isotopen-scintigrafie van de schildklier of voor een behandeling met radioactief jodium.

## Overwegingen

Iodine-based contrast medium (ICM) is administered during a CT-scan in volumes of 60-150 ml with iodine concentrations of 270-400 mg iodine (mgI) per ml. The total iodine dose of the ICM with organically bound iodine that is administered is between 16,000 and 60,000 mgI. Since ICM are excreted unchanged in the urine and are not metabolized, this iodine load will not be available to the thyroid. More important is that bottles of ICM contain small amounts of inorganic free iodide, depending on shelf-life and exposure to light, which might be directly available for thyroid uptake. Concentrations are in the range of 0,002-0,03 mgI/ml and as a result, an amount of approximately 0.1-4.5 mgI free iodide will be injected (0,001-0,007% of the amount of injected organically bound iodine) (Rendl, 2001; van der Molen, 2004). This amount is about 1-30 times the recommended daily allowance for iodine of 150 mg. A recent study, however, showed no increased levels of free iodide in the thyroid glands of ICM-treated animals (Hichri, 2020).

In a nested case-control study it was found that ICM exposure was associated with a risk of hyperthyroidism

(defined as TSH < 0.1 mU/l; OR 2.50, 95%CI 1.06-5.93) and a risk of hypothyroidism (defined as TSH>10 mU/l; OR 3.05, 95%CI 1.07-8.72) (Rhee, 2012). In a recent meta-analysis, however, it was shown that the absolute risk of IIHT was very low with an estimated prevalence of 0.1% (95%CI 0.0-0.6%) (Bervini, 2021). IIHT develops when the normal response to excess iodine with acute inhibition of the organification of iodine (i.e., acute Wolff-Chaikoff effect), is impaired. Risk factors include nontoxic diffuse or nodular goiter, latent Graves' disease, and long-standing iodine deficiency.

The reported prevalence of overt iodine induced hypothyroidism ranges from 0-8.1% (Bednarczuk, 2021). It develops when the thyroid fails to escape from the acute Wolff-Chaikoff effect, which may occur in euthyroid patients with a wide variety of thyroid disorders such as previous Hashimoto's thyroiditis, Graves' disease, thyroiditis, or previous thyroid surgery (Lee, 2015). It should be noted that published studies on prevalence are highly heterogeneous with respect to background iodine intake, selection of patients with or without previous history of thyroid disease, sample size, type of radiological examination, definition of thyroid disease and follow-up period. There are several case reports of iodine- induced thyrotoxicosis describing complications such as atrial fibrillation, heart failure or even thyroid storm (See Bednarczuk 2021, Table 2).

The efficacy of prophylactic treatment for development of iodine-induced hyperthyroidism has not been convincingly demonstrated. The randomised study by Nolte (Nolte, 1996) did not show a reduction of IIHT in the prophylactic treatment group, but that study was clearly underpowered. The study by Fricke (Fricke, 2004) was not randomised and compared two different subpopulations which were selected to receive prophylactic treatment or not based on TSH level and $^{99m}$Technetium thyroid uptake. Despite prophylactic treatment, two patients developed iodine induced hyperthyroidism. It should be noted, however, that the study by Fricke (2004) did not contain a comparable control group without prophylactic treatment.

The European Thyroid Association (ETA) has recently issued a guideline for the management of iodine-based contrast media-induced thyroid dysfunction (Bednarczuk, 2021). In view of the lack of well-designed studies in this field and to prevent conflicting statements as much as possible, we decided to adopt several of the ETA guideline recommendations.

In view of the low incidence of iodine-induced thyroid dysfunction, the usually mild symptoms and the self-limiting clinical course, routine testing of the thyroid function is not indicated before ICM administration. Baseline testing of thyroid function might be considered in patients at risk for development of iodine induced hyperthyroidism with a complicated clinical course, i.e., patients older than 65 years with clinically severe cardiovascular morbidity (Bednarczuk, 2021). Overt hyperthyroidism is generally considered an absolute contraindication to ICM administration, and alternative imaging, like MRI or ultrasound, is then recommended. In emergency cases, prophylactic treatment should be initiated. Subclinical hyperthyroidism is not a contra-indication for ICM administration. In patients older than 65 years with severe cardiovascular morbidity and subclinical hyperthyroidism, prophylactic treatment might be considered. A more conservative approach would be to measure thyroid function (TSH, FT4) 3-4 weeks after ICM administration. A commonly used prophylactic treatment protocol is thiamazole 30 mg once daily, started the day before ICM administration and continued for 14 days. It has been suggested that combination with potassium perchlorate (500mg twice a day) would be more effective. Treatment with thiamazole is usually well tolerated. Adverse

effects are predominantly skin allergy (maculopapular rash, urticaria) and arthralgias. The most important adverse effect of potassium/sodium perchlorate is agranulocytosis, but this is a rare event (about 1 in 275 patients) and occurs predominantly at daily dosages above 1000mg given for several months.

Baseline subclinical hypothyroidism and overt hypothyroidism are not a contraindication to ICM administration.

Yet another relevant question in clinical practice is the minimal interval required between ICM injection and isotope imaging of the thyroid or radioactive iodine (RAI) treatment. The administration of ICM is known to suppress thyroidal RAI uptake, lasting for several weeks (Nygaard, 1998). Some studies on urinary iodine secretion after ICM administration for outpatient CT scans indicate that 75% of patients' values returned to baseline within 5–6 weeks and 90% within 11 weeks (Lee 2015, Nimmons, 2013). A study performed in post-thyroidectomy patients requiring RAI treatment demonstrated that 1 month is sufficient for urinary iodine to return to its baseline value after the use of ICM (Padovani, 2012). These results may be used to guide the timing of RAI treatment as well as diagnostic scintigraphy with radioactive iodine or Tc-99m-pertechnetate following contrast exposure. The American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer (2015) state that concerns about iodine burden from IV contrast agents causing a clinically significant delay in subsequent whole-body scans or RAI treatment post-thyroidectomy is generally unfounded, as iodine is generally cleared within 4-8 weeks in most patients (Haugen, 2016). In doubtful situations, a spot or 24-h urinary iodine level may be checked before isotope studies. In line with the ETA guideline (Bednarczuk, 2021), we recommend postponing isotope imaging of the thyroid and RAI treatment for 4 to 8 weeks after ICM injection, or to withhold ICM administration 4 to 8 weeks before a planned RAI treatment.

**Recommendations**

*In view of the low incidence of iodine induced thyroid dysfunction, the usually mild symptoms, and the self-limiting clinical course, routine testing of the thyroid function is not indicated before ICM administration. These recommendations are in line with the* ETA guideline *(Bednarczuk, 2021).*

| |
|---|
| Do not routinely measure the thyroid function before administration of iodine-based contrast media.<br><br>Consider measurement of thyroid function in high-risk patients for iodine-induced hyperthyroidism, especially in subjects older than 65 years and those with severe cardiovascular morbidity. |

*In patients older than 65 years with severe cardiovascular morbidity and subclinical hyperthyroidism, prophylactic treatment might be considered. These recommendations are in line with the* ETA guideline *(Bednarczuk, 2021).*

| |
|---|
| Consider prophylactic treatment prescribed by an internal medicine specialist in selected patients with subclinical hyperthyroidism receiving iodine-based contrast media (e.g., patients older than 65 years or severe cardiovascular morbidity), starting one day before contrast administration and continuing for 14 days with thiamazole 30 mg once daily and possible addition of potassium perchlorate 500 mg twice daily. |

*After ICM injection, the iodine uptake by the thyroid gland is temporarily suppressed. Therefore, isotope*

*imaging of the thyroid or RAI should be postponed after ICM injection. These recommendations are in line with the* ETA guideline *(Bednarczuk, 2021).*

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| Avoid isotope imaging of the thyroid and/or radioactive iodine treatment for 4-8 weeks after iodine-based contrast media injection or withhold iodine-based contrast media administration for 4-8 weeks before planned isotope imaging of the thyroid or radioactive iodine treatment. |

## Onderbouwing

### Achtergrond

Iodine-based contrast media (ICM) contain substantial amounts of iodine which might result in iodine-induced hyperthyroidism (IIHT) or iodine-induced hypothyroidism. Depending on the magnitude of this risk and the clinical implications, prophylactic medication could be considered.

### Conclusies / Summary of Findings

| | |
|---|---|
| **Very low GRADE** | The evidence is very uncertain about the effect of prophylactic drugs on the prevention of IIHT in patients with indication for iodinated contrast media administration and<br><br>• From a low iodine area (very low GRADE).<br>• With thyroid disease (very low GRADE).<br><br>*Fricke, 2004; Nolte, 1996* |

### Samenvatting literatuur

Description of studies

**Randomized controlled study**

Nolte et al. (1996) performed a prospective randomized study aiming to investigate the efficacy of prophylactic application of thyrostatic drugs in patients with subclinical hyperthyroidism undergoing elective coronary angiography. The authors screened patients for TSH who were admitted to the hospital for coronary angiography. Patients lived in an area of moderate iodine deficiency. Inclusion criteria were age between 40-75 years, TSH levels < 0.4 mU/L, normal FT3-index, normal FT4-index, and a normal $^{99m}$Technetium-uptake. Those with manifest hyperthyroidism, large autonomous thyroid adenoma, immune related thyroid disease, urine iodine excretion > 200 mmol/mol creatinine, unstable angina pectoris or a Karnofsky Index < 50% were excluded. In addition, patients were also excluded if they were using thyroid hormones, thyrostatic drugs or amiodarone or had received contrast media during the previous 6 months. In total 51 patients fulfilled the criteria and were randomly assigned to one of three groups (17 patients in each group): group 1 received 20 mg of thiamazole once a day, group 2 was treated with 900 mg of sodium perchlorate (300mg 3 times a day) and group 3 received no special therapy. The treatment started 1 day before coronary angiography and lasted for 14 days. During angiography, patients were exposed to a mean contrast volume of 149ml, ranging from 50 to 410 ml. The three groups were comparable in age, sex, mean volume of contrast and goitre size. There were no side effects reported from the thyrostatic drugs. Follow up assessment was done 30 days after

coronary angiography. Nolte (1996) defined IIHT as suppressed TSH (<0.4 mU/l) and increased FT4-index and/or FT3-index. Nolte (1996) defined iodine-induced hypothyroidism as increased TSH and reduced FT4-index 30 days after coronary angiography.

**Prospective interventional study**
Fricke et al. (2004) performed a prospective study that had the objective to identify which patients with subclinical hyperthyroidism should receive prophylactic medication before coronary angiography to prevent IIHT. The authors screened all patients admitted for coronary angiography and included all patients with a basal TSH level of less than 0.3 mU/l and normal levels of T3 and FT4. Patients with thyroid antibodies or using medication for thyroid disease were excluded. Additional exclusion criteria were use of amiodarone, renal insufficiency (serum creatinine >133 mmol/l) or administration of contrast agents during the previous 3 months. Indication for prophylactic drug treatment was determined by the TSH level and the results of $^{99m}$Technetium scintigraphy. No prophylactic medication was given to patients with 1) homogenous tracer distribution in the thyroid, $^{99m}$Technetium thyroid uptake (TCTU) less than 1.5%, and TSH ranging from 0.05 to less than 0.3 mU/l; 2) homogenous tracer distribution in the thyroid, TCTU less than 1.0%, and TSH less than 0.05 mU/l; and 3) focal uptake and TCTU less than 1.0%. All other patients received 900 mg perchlorate (divided in 3 doses per day) for 2 weeks, starting at least 3 hours before coronary angiography. Thiamazole was added depending on the volume of the autonomous thyroid volume: 20 mg for 7 days in case of a volume of 5- 10 ml, and 60 mg thiamazole in the first week followed by 20 mg in the second week in case of a volume > 10 ml. Age was no selection criterion, mean age was 65±8.7 years. Coronary angiography was performed with an average of 157(±85 ml) iopromide containing 370 mg iodine per ml. In total 56 patients underwent coronary angiography without and 19 patients with prophylactic medication, i.e., 6 patients perchlorate only and 13 patients perchlorate combined with thiamazole. Follow up assessment was done at 1, 14, and 28 days after coronary angiography. This paper did not specifically define IIHT.

Results
Results will be described separately for the previously described subgroups.

1. *Iodine-induced hyperthyroidism (IIHT)*

The prospective randomized controlled study by Nolte (1996) reported one case of IIHT in the thiamazole group (1/17), one case in the perchlorate group (1/17), and two cases in the control group (2/17). Thyroid hormone levels were only slightly elevated in all cases. Only two persons developed mild clinical symptoms of hyperthyroidism, one in the thiamazole group and one in the perchlorate group, but none of these needed treatment with thyrostatic drugs.

The prospective interventional study by Fricke (2004) reported two cases of IIHT in the group receiving prophylactic drug treatment (2/19). In one case prophylactic drug treatment had to be stopped because of side effects, which was followed by development of hyperthyroidism. In the other case, the patient

demonstrated mild hyperthyroidism the day after coronary angiography despite prophylactic treatment with perchlorate, which was stabilized within a few days with the administration of thiamazole (Fricke, 2004). There we no cases of IIHT in the group of 56 patients who did not receive prophylactic drug treatment.

*TSH, thyroid hormones and* $^{99m}$Technetium-uptake
The prospective randomized controlled study by Nolte (1996) measured TSH, delta TSH (response 30 min after 200µg of TRH i.v.), mean FT4-index, mean FT3-index and $^{99m}$Technetium-uptake at baseline and after follow-up of 30 days. The authors reported a significant decrease in TSH and increase in FT4- and FT3-index in the control group, whereas these values remained unchanged in the intervention groups or showed a slight increase (TSH in the thiamazole group). Alterations of $^{99m}$Technetium-uptake were minimal in both intervention groups but was significantly reduced in the control group after 30 days.

*TSH and free thyroxine*
The prospective interventional study by Fricke (2004) reported TSH, FT4 and T3 at baseline and at 1, 14 and 28 days after coronary angiography. Within the group receiving prophylactic treatment (n=19), two cases of hyperthyroidism occurred. One patient developed IIHT after interruption of the prophylactic treatment because of side effects. The other patient demonstrated mild IIHT the day after ICM administration despite prophylactic treatment with perchlorate, which was quickly resolved after addition of thiamazole. The remaining 17 patients in the prophylactic treatment group showed stable TSH and T3 levels, except for a slight TSH increase and T3 decrease at day 28. In this group, FT4 was slightly elevated at day 14 and slightly decreased at day 28. The group without prophylactic treatment (n=56) showed an increase of TSH at day 1 and day 14, with an increase of FT4 day 14 and day 28 and a transient decrease in T3 at day 1 All changes in TSH, FT4 and T3 were within the reference range.

2. *Iodine induced hypothyroidism*

The prospective randomized study by Nolte (1996) found no cases of iodine-induced hypothyroidism 30 days after coronary angiography. Fricke (2004) did not report this outcome measure.

Level of evidence of the literature
Observational studies start at a low GRADE. Note: interventional studies.

The level of evidence regarding the outcome measure IIHT started on a low GRADE and was further downgraded to a very low GRADE levels because of study limitations (risk of bias) and the number of included patients (imprecision).

## Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: What are strategies for the prevention of IIHT, with a special interest in patients described above.

**P** (Patient): Patients with an indication of ICM administration with a special interest for the subgroups described above.

**I** (Intervention): Prevention strategy for IIHT: methimazole (synonym: thiamazole), propylthiouracil, perchlorate.
**C** (Comparison): No prevention strategy for IIHT or different prevention strategy.
**O** (Outcomes): Iodine-induced hyperthyroidism, iodine-induced hypothyroidism.

**Relevant outcome measures**
The guideline development group considered iodine-induced hyperthyroidism (IIHT) as a critical outcome measure for decision making, and iodine-induced hypothyroidism as important outcome measures for decision making.

The working group defined the outcome measures as follows: iodine-induced hyperthyroidism is the clinical condition of hyperthyroidism (e.g., palpitations, tremulousness, heat intolerance) caused by iodinated contrast media, which usually occurs weeks or months after its administration (Bednarczuk, 2021; Bervini, 2021). Iodine-induced hypothyroidism is the clinical condition of hypothyroidism (e.g., fatigue, weight gain, cold intolerance) caused by iodinated contrast media, which usually occurs weeks or months after its administration. Both iodinated contrast media induced hyperthyroidism and hypothyroidism are usually self-limiting conditions and resolve within weeks to months.

The working group did not define a minimal clinical important difference beforehand, because it is unclear what the prevalence of IIHT is in the no-prevention-strategy group (control group) with risk factors for IIHT (the previously described groups at risk for IIHT). Because literature about the subject is scarce, it was decided to provide only a descriptive analysis.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until July 7th, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 188 hits. Studies were selected based on the following criteria: studies with comparative design, comparing different prevention strategies for IIHT in the previously described subgroups. Forty-two studies were initially selected based on title and abstract screening. After reading the full text, forty studies were excluded (see Table of excluded studies in 'Appendices to modules'), and two studies were included.

Results
Two studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

## Referenties

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# Veilige tijdsintervallen en analytische interferentie

## Verantwoording

Laatst beoordeeld :

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

# Meerdere onderzoeken met contrastmiddelen bij patiënten met normale of gereduceerde nierfunctie

## Uitgangsvraag

Wat is een veilig tijdsinterval bij patiënten met een verminderde nierfunctie tussen twee radiologische of cardiologische onderzoeken?

Wat is een veilig tijdsinterval bij patiënten met een verminderde nierfunctie en:

1. Twee onderzoeken met jodiumhoudend contrastmiddel (CM)?
2. Twee onderzoeken met gadoliniumhoudend CM?
3. Twee onderzoeken met jodiumhoudend- en gadoliniumhoudend CM?

Deze vraag bevat de volgende subgroepen:

- Electieve CT/Angio/MRI bij patiënten met een normale nierfunctie (eGFR >60 ml/min/1.73m$^2$)
- Electieve CT/Angio/MRI bij patiënten matig verminderde nierfunctie (eGFR 30-60 ml/min/1.73m$^2$)
- Electieve CT/Angio/MRI bij patiënten met ernstig verminderde nierfunctie (eGFR < 30 ml/min/1.73m$^2$)
- CT/Angio/MRI bij spoedeisende of levensbedreigende situaties

## Aanbeveling

1. Veilig tijdsinterval tussen radiologische of cardiologische onderzoeken met jodiumhoudende CM

Overweeg een wachttijd tussen **electieve** CM-versterkte CT of (coronair) angiografie onderzoeken met meerdere jodiumhoudende CM-toedieningen bij patiënten met een **normale nierfunctie** (eGFR>60 ml/min/1.73m$^2$) van:

- Optimaal 12 uur (bijna complete eliminatie van vorig toegediend jodiumhoudend CM)
- Minimaal 4 uur (als de klinische indicatie een snelle follow up vereist)

Overweeg een wachttijd tussen **electieve** CM-versterkte CT of (coronair) angiografie onderzoeken met meerdere jodiumhoudende CM-toedieningen bij patiënten met een **matig verminderde nierfunctie** (eGFR 30-60 ml/min/1.73m$^2$) van:

- Optimaal 48 uur (bijna complete eliminatie van vorig toegediend jodiumhoudend CM)
- Minimaal 16 uur (als de klinische indicatie een snelle follow up vereist)

Overweeg een wachttijd tussen **electieve** CM-versterkte CT of (coronair) angiografie onderzoeken met meerdere jodiumhoudende CM-toedieningen bij patiënten met een **ernstig verminderde nierfunctie** (eGFR <30 ml/min/1.73m2) van:

- Optimaal 168 uur (bijna complete eliminatie van vorig toegediend jodiumhoudend CM)
- Minimaal 60 uur (als de klinische indicatie een snelle follow up vereist

Bij **spoedeisende of levensbedreigende situaties**, houd minder wachttijd aan tussen CM-versterkte onderzoeken met opeenvolgende jodiumhoudende CM-toedieningen.

2. Veilig tijdsinterval tussen radiologische onderzoeken met gadoliniumhoudende CM

Overweeg een wachttijd tussen **electieve** CM-versterkte MRI onderzoeken met meerdere gadoliniumhoudende CM bij patiënten met een **normale nierfunctie** (eGFR>60 ml/min/1.73m$^2$) van:

- Optimaal 12 uur (bijna complete eliminatie van het vorig toegediende gadoliniumhoudende CM)
- Minimaal 4 uur (als de klinische indicatie een snelle follow up vereist)

Overweeg een wachttijd tussen **electieve** CM-versterkte MRI onderzoeken met meerdere gadoliniumhoudende CM-toedieningen bij patiënten met een **matig verminderde nierfunctie** (eGFR 30-60 ml/min/1.73m$^2$) van:

- Optimaal 48 uur (bijna complete eliminatie van vorig toegediend gadoliniumhoudend CM)
- Minimaal 16 uur (als de klinische indicatie een snelle follow up vereist)

Overweeg een wachttijd tussen **electieve** CM-versterkte MRI onderzoeken met meerdere gadoliniumhoudende CM-toedieningen bij patiënten met een **ernstig verminderde nierfunctie** (eGFR <30 ml/min/1.73m$^2$) van:

- Optimaal 168 uur (bijna complete eliminatie van vorig toegediende gadoliniumhoudende CM)
- Minimaal 60 uur (als de klinische indicatie een snelle follow up vereist)

Bij **spoedeisende of levensbedreigende situaties**, houd minder wachttijd aan tussen contrast- versterkte onderzoeken met opeenvolgende gadoliniumhoudende CM-toedieningen.

3. Veilig tijdsinterval tussen radiologische of cardiologische onderzoeken met jodiumhoudende en gadoliniumhoudende CM

Bij CT of (coronair) angiografie met jodiumhoudend CM en MRI met gadoliniumhoudend CM op dezelfde dag in **electieve** situaties, is het beter om met het MRI-onderzoek te starten, behalve als het CT onderzoek voor de nieren, ureters of blaas bedoeld is (CT Urografie).

Overweeg een wachttijd tussen een **electieve** MRI met gadoliniumhoudend CM en een CT of (coronair) angiografie met jodiumhoudend CM bij patiënten met **een normale nierfunctie** (eGFR >60 ml/min/1.73m$^2$) van:

- Optimaal 6 uur (bijna complete eliminatie van vorig toegediende gadoliniumhoudende CM)
- Minimaal 2 uur (als de klinische indicatie een snelle follow up vereist)

Overweeg een wachttijd tussen een **electieve** MRI met gadoliniumhoudend CM en een CT of (coronair) angiografie met jodiumhoudend CM bij patiënten met **een matig verminderde nierfunctie** (eGFR 30-60 ml/min/1.73m$^2$) van:

- Optimaal 48 uur (bijna complete eliminatie van vorig toegediende gadoliniumhoudende CM)
- Minimaal 16 uur (als de klinische indicatie een snelle follow up vereist)

Overweeg een wachttijd tussen een **electieve** MRI met gadoliniumhoudend CM en een CT of (coronair) angiografie met jodiumhoudend CM bij patiënten met **een ernstig verminderde nierfunctie** (eGFR <30 ml/min/1.73m$^2$) van:

- Optimaal 168 uur (bijna complete eliminatie van vorig toegediende gadoliniumhoudende CM)
- Minimaal 60 uur (als de klinische indicatie een snelle follow up vereist)

Bij CT of (coronair) angiografie met jodiumhoudend CM en MRI met gadoliniumhoudend CM op dezelfde dag in **spoedeisende of levensbedreigende situaties**, voer beide onderzoeken direct achter elkaar uit zonder wachttijd.

### Overwegingen

### 1. Pharmacokinetics and Elimination of Iodine-based CM

The physicochemical data of currently used ICM have been summarized in Supplemental Table S1 at the end of this guideline.

For ICM the use of an open, 2-compartment model is justified. No third compartment for storage can be identified. In patients with normal renal function the renal elimination half- value times are between 1.8 and 2.3 h (average 2.0h) Almost all the administered contrast medium will be cleared in 6 half-lives, or 12 h, and already over 75% will be cleared in 2 half- lives, or 4 h.

In patients with moderate renal impairment (eGFR 30-60 ml/min/1,73m$^2$), the renal elimination half-lives increase to 7 h, so it will need a maximum 42 h for near-complete clearance, and about 14 h for 75% clearance. In severe renal impairment (eGFR < 30 ml/min/1,73m$^2$) renal elimination half-lives vary widely between 10-27 h, so in the worst case it will need a maximum 162 h (6,75 days) for near-complete clearance, and about 55 h (2,3 days) for 75% clearance (Table 1).

**Table 1 Renal Excretion of Iodine-Based Contrast Media**

| ***Name*** | ***Structure*** | ***Ionicity*** | ***Renal Excretion*** | | |
|---|---|---|---|---|---|
| | | | *(Elimination T½; hours - Near complete elimination in 6 x T½)* | | |
| | | | Normal Renal Function | Moderately Reduced RF | Severely Reduced RF |
| | | | *(eGFR > 60 ml/min)* | *(eGFR 30-60 ml/min)* | *(eGFR < 30 ml/min)* |
| Iohexol | Monomeric | Nonionic | 2.0 | NA | 27.2 |
| Iopromide | Monomeric | Nonionic | 1.8 | NA | NA |
| Iomeprol | Monomeric | Nonionic | 2.3 | 6.9 | 15.1 |
| Ioversol | Monomeric | Nonionic | 2.1 | NA | NA |
| Iobitridol | Monomeric | Nonionic | NA | NA | NA |
| Iodixanol | Dimeric | Nonionic | 2.2 | NA | 23.0 |

*Sources: See references in text above*

### *2. Pharmacokinetics and Elimination of Gadolinium-based CM*

The physicochemical data of currently available GBCA have been summarized in Supplemental Table S2 at the end of this guideline.

For general MRI, currently only stable macrocyclic GBCA are allowed. Using the optimized open 3-compartment model, in patients with normal renal function the renal elimination half-lives are between 1.3 and 1.8 h (average 1.6h) and the residual excretion time will be in

the order of 6 h. Almost all the administered contrast medium will be cleared in 6 half-lives, or 10-12 h, and already over 75% will be cleared in a little more than 2 half-lives, or 4 h.

In patients with moderate renal impairment (eGFR 30-60 ml/min/1,73m$^2$), the renal elimination half-lives increase to 4-7 h, so it will need a maximum 42 h for near-complete clearance, and about 14 h for 75% clearance. As the residual excretion depends on thermodynamic stability, it will not be significantly prolonged in these patients.

The situation is worse for patients with severe renal impairment (eGFR < 30 ml/min/1,73m$^2$). Renal elimination half-lives are between 10-30 h, so it will need a maximum 180 h (7,5 days) for near-complete clearance, and about 60 h (2,5 days) for 75% clearance. It is thus far unclear if the residual excretion is prolonged in these patients (Table 2).

**Table 2 Renal Excretion of Gadolinium-Based Contrast Agents**

| ***Name*** | ***Ligand*** | ***Structure*** | ***Ionicity*** | ***Renal Excretion*** | | |
|---|---|---|---|---|---|---|
| | | | | *(Elimination T½; hours – Near complete elimination in 6 x T½)* | | |
| | | | | Normal RF | Moderately Reduced RF | Severely Reduced RF |
| | | | | *(eGFR > 60 ml/min)* | *(eGFR 30-60 ml/min)* | *(eGFR < 30 ml/min)* |
| Gadopentetate | DTPA | Linear | Ionic | 1.6 | 4.0 | 30.0 |
| Gadobenate | BOPTA | Linear | Ionic | 1.2-2.0 | 5.6 | 9.2 |
| Gadoxetate | EOB-DTPA | Linear | Ionic | 1.0 | 2.2 | 20.0 |
| Gadoteridol | HP-DO3A | Macrocyclic | Nonionic | 1.6 | 6.9 | 9.5 |
| Gadobutrol | BT-DO3A | Macrocyclic | Nonionic | 1.8 | 5.8 | 17.6 |
| Gadoterate | DOTA | Macrocyclic | Ionic | 1.6 | 5.1 | 13.9 |
| Gadopiclenol | NA | Macrocyclic | Nonionic | 1.6-1.9 | 3.8 | 11.7 |

Sources: from references in text above

For approved linear hepatobiliary GBCA, moderate renal impairment leads to an increase in renal elimination half-value times of 2-5 h, corresponding to a maximum 30h for near- complete and 10h for 75% clearance. Severe renal impairment leads to an increase in renal elimination half-value times of 10-20 h, corresponding to 60-120 h for near-complete and 20-40 h for 75% clearance. Residual excretion half-lives are in the order of 30-48h.

### *3. Combined Enhanced imaging with an ICM and a GBCA*

In oncology diagnosis and follow-up, contrast-enhanced MRI examinations with GBCA and contrast-enhanced CT examinations with ICM are often combined, sometimes on the same day. The presence of ICM will influence the (results of) MRI examination and the presence of GBCA will influence the (results of) CT examination. The degree of these effects will determine the optimal order of examinations. The pharmacokinetics of both types of CM will dictate how waiting times between examinations should be scheduled.

*Combining CT and MRI: Effects of GBCA on CT studies*

Multiple in vitro studies have demonstrated the effect of GBCA in CT. At equal mass concentration, GBCA will have a higher CT attenuation than ICM due to the higher atomic number of Gadolinium (64) compared to iodine (53) (Bloem, 1989; Engelbrecht, 1996; Gierada, 1999; Kim, 2003; Quinn, 1994; Schmitz, 1995; Schmitz, 1997; Zwicker, 1991).

Yet, in clinical practice the molar concentration used for ICM is much higher than for GBCA. For instance, iopromide 300 mgI/ml equals 2,94 mmol/ml, compared to GBCA with 0.5-1.0 mmol/ml. Excellent detailed phantom studies from Sweden focusing on equal attenuation have shown that in CT at 80-140kVp a solution of 0.5M GBCA is iso-attenuating to a solution of ICM with 91-116 mg I/mL for a chest phantom, and to 104-125 mg I/mL for an abdominal phantom. Due to a different X-ray tube filtration, in DSA at 80-120 kVp a solution of 0.5M GBCA is iso-attenuating to 73-92 mg I/mL (Nyman, 2002 and 2011).

Many clinical studies have used GBCA for CT or angiography in renal insufficiency patients or in patients with (severe) hypersensitivity reactions to ICM. The GBCA injection frequently needs high doses of 0.3-0.5 mmol/kg for good vascular enhancement (Kaufman 1996), which is relatively short-lived. Such doses may be useful for vascular imaging or interventions but are usually not suitable for optimal imaging of the abdominal organs. Good overviews of the results can be found in multiple reviews (Spinosa, 2002; Strunk, 2004).

Nowadays, such high doses cannot be used anymore. Animal studies have shown that for equal attenuation, GBCA are more nephrotoxic and more costly than low-dose or diluted ICM (Elmsthål, 2006; Nyman, 2011). In addition to the risk of NSF and Gadolinium deposition, these are the major reasons that current ESUR guidelines strongly discourage the use of GBCA for radiographic examinations (Thomsen, 2002).

Due to the short-lived effect of GBCA injection in CT, this vascular enhancement is less cumbersome in clinical practice when combining contrast-enhanced CT and MRI examinations on the same day. One exception is that the kidneys will concentrate the gadolinium, so that the renal collecting systems, ureters, and bladder will show CT enhancement for a significant period.

*Combining CT and MRI: Effects of ICM on MRI studies*

In vitro experiments in MR Arthrography may serve as a model of these effects. Mixing of ICM with GBCA will lead to some shortening of the T1 (spin-lattice) relaxation time, and a more profound shortening of the T2 (spin-spin) relaxation time. This results in an increase in T1w signal and a decrease in T2w signal. The magnitude of the effect is greater for higher GBCA concentrations. The presence of ICM shifts the peak SI towards lower GBCA concentrations. Overall, in small joint spaces the enhancement was decreased (Andreisek, 2008; Choi, 2008; Ganguly, 2007; Kopka, 1994; Montgomery, 2002).

Similar effects can also be seen in routine MRI examinations, but to a lesser degree. The shortening effect on T1 and T2 times, with increase in T1w signal and a decrease in T2w signal, depends on the concentration of the ICM and on the side chains in the molecular structure of the specific ICM that is used (effect is for ioxithalamate > iotrolan > iopamidol > iodixanol, iohexol or iomeprol) (Hergan, 1995; Jinkins, 1992; Kopka, 1994; Morales, 2016). Very recently it was shown that adding an overdose of ICM to macrocyclic GBCA led to a significant increase in R1 relaxation and the combination was excreted more slowly, possibly because of the

formation of chemical adducts between the lipophilic three-iodo-benzene rings of the ICM and the tetra-aza-cycle of the macrocyclic GBCA (DiGregorio, 2022). Increasing concentrations of ICM will also influence diffusion weighted imaging, with increased signal and decreased ADC values (Ogura, 2009), and on functional imaging with shortening of the T2* times used in BOLD MRI (Wang, 2014).

The effects of ICM in MRI can be longer-living and will be more disturbing on subsequent contrast-enhanced MRI.

**Recommendations**

**1. Safe time intervals in enhanced imaging with iodine-based contrast media**

*Based on the following, the Committee can recommend the following waiting times between successive administrations of iodine-based contrast media in contrast-enhanced CT (or (coronary) angiography) to avoid accumulation of iodine-based contrast media with potential safety issues:*

Consider a waiting time between **elective** contrast-enhanced CT or (coronary) angiography with successive iodine-based contrast media administrations in patients with **normal renal function** (eGFR >60 ml/min/1.73m$^2$) of:

- Optimally 12 hours (near complete clearance of the previously administered iodine-based contrast media)
- Minimally 4 hours (if clinical indication requires rapid follow-up)

Consider a waiting time between **elective** contrast-enhanced CT or (coronary) angiography with successive iodine-based contrast media administrations in patients with **moderately reduced renal function** (eGFR 30-60 ml/min/1.73m$^2$) of:

- Optimally 48 hours (near complete clearance of the previously administered iodine- based contrast media)
- Minimally 16 hours (if clinical indication requires rapid follow-up)

Consider a waiting time between **elective** contrast-enhanced CT or (coronary) angiography with successive iodine-based contrast media administrations in patients with **severely reduced renal function** (eGFR < 30 ml/min/1.73m$^2$) of:

- Optimally 168 hours (near complete clearance of the previously administered iodine-based contrast media)
- Minimally 60 hours (if clinical indication requires rapid follow-up)

In **emergency or life-threatening situations**, employ less waiting time between contrast- enhanced CT (or coronary angiography) with successive iodine-based contrast media administrations.

### 2. Safe time intervals in enhanced imaging with gadolinium-based contrast agents

*Based on the review above, the Committee recommends the following waiting times between contrast-enhanced MRI with successive administrations of gadolinium-based contrast agents, to avoid accumulation of gadolinium-based contrast agents with potential safety issues:*

Consider a waiting time between **elective** contrast-enhanced MRI with successive gadolinium-based contrast agent administrations in patients with **normal renal function** (eGFR >60 ml/min/1.73m$^2$) of:

- Optimally 12 hours (near complete clearance of the previously administered gadolinium-based contrast agent)
- Minimally 4 hours (if clinical indications require rapid follow-up)

Consider a waiting time between **elective** contrast-enhanced MRI with successive gadolinium-based contrast agent administrations in patients with **moderately reduced renal function** (eGFR 30-60 ml/min/1.73m$^2$) of:

- Optimally 48 hours (near complete clearance of the previously administered gadolinium-based contrast agent)
- Minimally 16 hours (if clinical indications require rapid follow-up)

Consider a waiting time between **elective** contrast-enhanced MRI with successive gadolinium-based contrast agent administrations in patients with **severely reduced renal function** (eGFR < 30 ml/min/1.73m$^2$) of:

- Optimally 168 hours (near complete clearance of the previously administered gadolinium-based contrast agent)
- Minimally 60 hours (if clinical indications require rapid follow-up)

In **emergency or life-threatening situations,** employ less waiting time between contrast- enhanced MRI with successive gadolinium-based contrast agent administrations.

### 3. Safe time intervals in combined enhanced imaging with an iodine-based contrast medium and a gadolinium-based contrast agent

*Based on the review above, the Committee recommends the following waiting times between contrast-enhanced MRI and contrast-enhanced CT or (coronary) angiography, to avoid interference of the contrast medium used in the first contrast-enhanced examination on the other contrast-enhanced examination, and to avoid accumulation of contrast media with potential safety issues:*

When combining contrast-enhanced CT or (coronary) angiography with an iodine-based contrast medium and contrast-enhanced MRI with a gadolinium-based contrast agent on the same day in **elective** situations, it is better to start with the MRI examination, unless the CT examination is intended for the kidneys, ureters, or bladder (CT Urography).

*In patients with normal renal function the interference of the contrast medium used in the first contrast-enhanced examination on the second contrast-enhanced examination will predominantly determine the suggested waiting times.*

Consider a waiting time between **elective** contrast-enhanced MRI with a gadolinium-based contrast agent and contrast-enhanced CT or (coronary) angiography with an iodine- based contrast medium in patients with **normal renal function** (eGFR >60 ml/min/1.73m$^2$) of:

- Optimally 6 hours (near complete clearance of the effects of the previously administered gadolinium-based contrast agent)
- Minimally 2 hours (if the clinical indication requires rapid follow-up)

*In patients with reduced renal function the avoidance of accumulation of contrast media with potential safety issues will predominantly determine the suggested waiting times (as in sections 1 and 2 above).*

Consider a waiting time between **elective** contrast-enhanced MRI with a gadolinium-based contrast agent and contrast-enhanced CT or (coronary) angiography with an iodine- based contrast medium in patients with **moderately reduced renal function** (eGFR 30-60 ml/min/1.73m$^2$) of:

- Optimally 48 hours (near complete clearance of the previously administered gadolinium-based contrast agent)
- Minimally 16 hours (if the clinical indication requires rapid follow-up)

Consider a waiting time between **elective** contrast-enhanced MRI with a gadolinium-based contrast agent and contrast-enhanced CT or (coronary) angiography with an iodine- based contrast medium in patients with **severely reduced renal function** (eGFR < 30 ml/min/1.73m$^2$) of:

- Optimally 168 hours (near complete clearance of the previously administered gadolinium-based contrast agent)
- Minimally 60 hours (if the clinical indication requires rapid follow-up)

When combining contrast-enhanced CT or (coronary) angiography with an iodine-based contrast medium and contrast-enhanced MRI with a gadolinium-based contrast agent on the same day in **emergency or life-threatening situations**, employ no waiting time and perform back-to-back examinations.

## Onderbouwing

## Achtergrond

The pharmacokinetics of contrast media (CM) will dictate how waiting times between CT or MRI examinations should be scheduled. There are few dedicated studies about the optimal time between successive doses of CM in repeated contrast-enhanced studies (Kwon, 2021) or when contrast-enhanced CT or (coronary) angiography and contrast-enhanced MRI studies are done in succession.

## Samenvatting literatuur

### Systematic literature analysis

For this chapter it was decided not to perform a systematic literature analysis.

### Narrative literature analysis

Results will be discussed separately for the previously described subgroups:

1. Pharmacokinetics and Elimination of Iodine-based CM
2. Pharmacokinetics and Elimination of Gadolinium-based CM
3. Combined CT and MRI Examinations with ICM and GBCA

## 1. Pharmacokinetics and Elimination of Iodine-based CM

Most studies on iodine-based CM (ICM) have employed an open, 2-compartiment model for pharmacokinetic analyses. The first compartment is the plasma in which the molecules are being diluted and the second compartment is the extravascular extracellular space of the tissues where there is an effective capillary permeability, i.e., outside the brain. In this classical model the plasma concentration decays by distribution of the CM from plasma to the extracellular volume (distribution phase, slope a), and by elimination of the CM from plasma to urine by renal excretion (elimination phase, slope b).

The elimination phase is of interest as it defines the time when a second administration of the same product can be performed safely, with no risk of accumulation and potential toxicity (such as contrast-associated acute kidney injury). In theory, near-complete elimination to 1,5% of the original concentration is achieved within 6 elimination half-lives (T½ b) (Bourin, 1997; Dean, 1993).

*Results in Animal Studies*

In most animal studies the open, 2-compartment model describes the pharmacokinetics of ICM well. All ICM behave similarly in early distribution and excretion. In animal studies distribution volumes ranged 180-250 ml/kg, or between 21-25% of body weight. This indicates distribution within the extracellular fluid only. Renal excretion is species dependent, and is higher for rats, rabbits, and dogs, compared to monkeys and humans due to their higher weight normalized GFR. Elimination half-life times in rat studies range 20-25 minutes, in dogs 50-62 minutes, and in monkeys 71-83 minutes (Bourrinet, 1994; Coveney, 1989; Dencausse, 1996; Gardeur, 1980; Heglund, 1995; Lorusso, 1994; Morin, 1988; Mützel,1980; Mützel, 1983).

The excretion in urine within 4h is 60-85% and within 24h is 86-95%, depending on the animal species. The urinary excretion is complete within 48h. Excretion in faeces is species- dependent, less than 1% for dogs and up to 7% for rats (Bourrinet, 1994; Coveney, 1989; Dencausse, 1996; Gardeur, 1980; Heglund, 1995; Lorusso, 1994; Morin, 1988; Mützel, 1980; Mützel, 1983).

After oral ingestion, 1-2% of the ICM reaches the systemic circulation and is eliminated rapidly via the kidneys. The rest is eliminated in unchanged form with the faeces (Bourrinet, 1994; Mützel, 1983).

*Results in Human Studies – Normal Renal Function*

Pharmacokinetics in humans also worked well using an open 2-compartment model.
The distribution volumes in healthy volunteers and young patients were between 165-280 ml/kg, indicating a distribution in the extracellular volume. Distribution half-lives are rapid, in the range of 15-22 minutes. For currently available nonionic ICM, the elimination half- value times range 1.8-2.3 hours (Bourin, 1997; Edelson, 1984; Fountaine, 1996; Krause, 1994; Lorusso, 2001; McKinstry, 1984; Olsson, 1983; Spencer, 1996; Svaland, 1992; Wilkins, 1989), but may already increase to 3.25-4h in volunteers and patients of older age (Hartwig, 1989).

Excretion in urine is quick and independent of dose. About 80% of the dose will be eliminated within 4h, and 93-98% is excreted in 24h. There is limited faecal excretion, usually < 2-4%. Nonionic ICM are not metabolized, and there is no binding to plasma proteins.

The elimination half-lives for older ionic high-osmolar ICM that are still in use as oral ICM for fluoroscopy or CT are shorter than for current nonionic low-osmolar CM used for intravascular administration, in the range of 1.3-1.8h (Difazio, 1978; Feldman, 1984; Gardeur, 1980).

*Results in Human Studies – Renal Insufficiency*

In patients with renal impairment the half-lives of the ICM increase progressively. The literature on pharmacokinetics of currently available ICM in patients with renal insufficiency is scarce and patient categories vary. In moderate renal insufficiency (eGFR 30- 60 ml/min/1.73m$^2$) the elimination half-lives increase up to 6.9h, and in severe renal insufficiency (eGFR < 30 ml/min/1.73m$^2$) the half-lives vary for several ICM from 10.0h to 27.0h, depending on the degree of insufficiency. When renal function is impaired, biliary excretion will increase somewhat (Corradi, 1990; Lorusso, 2001; Nossen, 1995).

The summarized data are largely dependent on the study populations and settings and should be taken as a relative indication.

## 2. Pharmacokinetics and Elimination of Gadolinium-based CM

Most of the early elimination of extracellular GBCA is via renal excretion, and for the hepatobiliary GBCA (gadobenate or gadoxetate) there is additional biliary excretion.

The elimination phase is of interest as it defines the time when a second administration of the same or another GBCA can be performed safely, with lower risk of accumulation and potential toxicity (such as nephrogenic systemic fibrosis or gadolinium deposition). In theory, near-complete elimination to 1,5% of the original concentration is achieved within 6 elimination half-lives (T½ b) (Bourin, 1997; Dean, 1993).

*Results in Animal Studies – Normal renal and biliary function*

All extracellular GBCA behave similarly in early distribution and excretion, except for brain. Elimination half-lives in rat studies range 16-23 min and in rabbit and dog studies 45-60 min for all clinically administered GBCA doses (Allard, 1988; Harpur, 1993; Lorusso, 1999; Robic, 2019; Tombach, 2002; Tweedle, 1988; Vittadini, 1988; Vogler, 1995), with decreases in elimination with increasing age or presence of diabetes of rats (Michel, 1992). The decrease is first rapid and then progressively slower. Steady-state distribution volumes range 210-230 ml/kg, indicating distribution in the extracellular fluid (Allard, 1988; Harpur, 1993; Lorusso, 1999; Robic, 2019; Tombach, 2002; Tweedle, 1988; Vittadini, 1988; Vogler, 1995). More than 95% of the contrast is recovered in urine within 24h after administration. Only small fractions are excreted with bile into the faeces, usually < 4% within 24h.

For the hepatobiliary GBCA gadobenate and gadoxetate, there is additional biliary excretion. Like the renal elimination, this is species-dependent, and is high for rats and rabbits. The administration of these CM is associated with a choleretic effect. About 30-35% is eliminated with bile into faeces for gadobenate (Lorusso, 1999; Vittadini, 1988), and 63-68% for gadoxetate (Schuhmann-Gampieri, 1997). Biliary excretion has a capacity-limiting step with increasing doses, and maximum excretion is about 5 µmol/min · kg.

Clearance of macrocyclic GBCA from the brain is a slow process, both for cerebrum and cerebellum. Half-lives for elimination were 1.8-2.0 weeks in the first 6 weeks, and 6.3-8.3 weeks thereafter, slightly slower in cerebellum than in cerebrum (Frenzel, 2021).

*Results in Animal Studies – Renal and Hepatobiliary Insufficiency*

Only few studies with hepatobiliary GBCA have been done in rats with combinations of reduced renal and biliary function. With reduced biliary elimination there will be an increased renal elimination and vice versa. Injection of bromosulfophthalein (BSP) or bile duct ligation can reduce biliary excretion of gadobenate to 1-5%, with concomitant increase in urinary excretion of 66-83% (De Haën, 1995). Renal artery or bile duct ligation reduced elimination half value times of gadoxetate, but significantly more after renal artery ligation. Between 1-3% of CM remained in the body in these animals (Mühler, 1994 and 1995).

*Results in Human Studies – Normal Renal and Biliary Function*

Pharmacokinetic analyses of extracellular GBCA in volunteers showed renal clearances matching the glomerular filtration rate. The reported excretion half-lives range from 1.3 to

1.8h. Steady state distribution volumes are in range of 180-250 ml/kg. Clearance from plasma is rapid with 75-85% of the CM cleared within 4h, and 94-98% cleared within 24h (Hao, 2019; Le Mignon, 1990; McLachlan, 1992; Staks, 1994; Tombach, 2002 Van Wagoner
1993, Weinmann, 1984).

For the hepatobiliary gadoxetate the terminal half-lives ranged from 1.0h for young to 1.8h for older volunteers, with a balanced renal and biliary excretion. The biliary excretion is only saturated for high doses, not used in clinical practice (Gschwend, 2011; Hamm, 1995; Schuhmann-Gampieri, 1992). Due to the lower biliary excretion, gadobenate has a profile that is more like the extracellular GBCA. The half-value times were 1.2h for clinically used doses with distribution volumes of 170-218 ml/kg (Spinazzi, 1999).

*Results in Human Studies – Renal and Hepatobiliary Insufficiency*

In patients with renal impairment the half-lives of the extracellular GBCA increase progressively. However, the summarized data are dependent on the study populations and settings and should be taken as a relative indication.

In patients with mild renal insufficiency (eGFR 60-90 ml/min/1.73m$^2$) the half-life for the new GBCA gadopiclenol increased to 3.2h (Bradu, 2021). In moderate renal insufficiency (eGFR 30-60 ml/min/1.73m$^2$) the increase in half-lives was between 3.8 and 6.9h, depending on the amount of renal impairment, with higher values for lower eGFR. This is equivalent with a factor of 2.5-3.5x that of volunteers with normal renal function. In severe renal insufficiency (eGFR < 30 ml/min/1.73m$^2$), excluding dialysis, half-lives are between 9.5-30h, equivalent to 6-18x the value of volunteers with normal renal function (Bradu, 2021, Chachuat, 1992; Joffe, 1998; Schuhmann-Gampieri, 1991; Swan, 1999; Tombach, 2000 and 2001, Yoshikawa, 1997).

In the hepatobiliary GBCA, a combination of renal and hepatic impairment has been studied, as bile duct excretion is able to compensate for some renal function deterioration.
Moderate hepatic impairment did not change the plasma half-life, but severe hepatic impairment (like Child-Pugh C cirrhosis) led to slight increases of 2.6h for gadoxetate and
2.2h for gadobenate (Davies, 2002; Gschwend, 2011). For gadoxetate, moderate renal impairment could be compensated with a half-life of only 2.2h, but severe renal impairment led to a half-value time of 20h (Gschwend, 2011). In gadobenate moderate renal impairment increased the half-life to 5.6h and severe impairment to 9.2h. This is much more like the other extracellular GBCA (Swan, 1999).

*Results in Systematic Reviews*

Already in the late 1980s, biodistribution studies suggested that an open 3-compartment model may better fit the pharmacokinetic data of GBCA than the 2-compartment model. The first compartment is the plasma and the second and third compartments are the extravascular extracellular space of the tissues where there is an effective capillary permeability. The second and third compartments of the model are related to rapidly and slowly equilibrating tissues (storage compartment) (Wedeking, 1988 and 1990).

In a large systematic review of pharmacokinetic data, the 3-compartiment, open model better fitted the data,

with 3 phases of GBCA decay from plasma. Apart from the distribution phase (a) and rapid (renal) elimination phase (b), there is a slow residual excretion phase (g). After IV administration of GBCA, plasma levels of gadolinium fall rapidly, indicating a short distribution phase with an average half-life of 0.2 ± 0.1 h. Then, levels will decrease slower as renal elimination prevails, with half-lives 1.7 ± 0.5 h when measured in plasma and 2.6 ± 0.6 h in urine (Lancelot, 2016).

The third phase of decay from the storage compartment can only be demonstrated in urine at a time when concentrations in plasma have become undetectable. Calculated rate constant g values are 0.107/h for gadoterate, and 0.012/h for gadobenate, and 0.029/h for gadoxetate. The half-life for this residual excretion phase is about 5-8 times longer for currently approved linear GBCA (approximately 25 h) compared to a macrocyclic GBCA (6 h), with risk of dechelation or transmetallation. This residual phase is species-independent and its rate constant g is closely related to the thermodynamic stability of the GBCA molecule. The relative contribution of this slow elimination is not insignificant, being 21-35% for linear GBCA vs. 10% for macrocyclic GBCA. The exact locations of this third compartment are not completely clear, but Gd retention/deposition can be found in the brain, spleen, liver, kidney, skin, and bones (Lancelot, 2016).

## 3. Combined Enhanced imaging with an ICM and a GBCA

In oncology diagnosis and follow-up, contrast-enhanced MRI examinations with GBCA and contrast-enhanced CT examinations with ICM are often combined, sometimes on the same day. The presence of ICM will influence the (results of) MRI examination and the presence of GBCA will influence the (results of) CT examination. The degree of these effects will determine the optimal order of examinations. The pharmacokinetics of both types of CM will dictate how waiting times between examinations should be scheduled.

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Gierada, 1999; Kim, 2003; Quinn, 1994; Schmitz, 1995; Schmitz, 1997; Zwicker, 1991).

Yet, in clinical practice the molar concentration used for ICM is much higher than for GBCA. For instance, iopromide 300 mgI/ml equals 2,94 mmol/ml, compared to GBCA with 0.5-1.0 mmol/ml. Excellent detailed phantom studies from Sweden focusing on equal attenuation have shown that in CT at 80-140kVp a solution of 0.5M GBCA is iso-attenuating to a solution of ICM with 91-116 mg I/mL for a chest phantom, and to 104-125 mg I/mL for an abdominal phantom. Due to a different X-ray tube filtration, in DSA at 80-120 kVp a solution of 0.5M GBCA is iso-attenuating to 73-92 mg I/mL (Nyman, 2002 and 2011).

Many clinical studies have used GBCA for CT or angiography in renal insufficiency patients or in patients with (severe) hypersensitivity reactions to ICM. The GBCA injection frequently needs high doses of 0.3-0.5 mmol/kg for good vascular enhancement (Kaufman 1996), which is relatively short-lived. Such doses may be

useful for vascular imaging or interventions but are usually not suitable for optimal imaging of the abdominal organs. Good overviews of the results can be found in multiple reviews (Spinosa, 2002; Strunk, 2004).

Nowadays, such high doses cannot be used anymore. Animal studies have shown that for equal attenuation, GBCA are more nephrotoxic and more costly than low-dose or diluted ICM (Elmsthål, 2006; Nyman, 2011). In addition to the risk of NSF and Gadolinium deposition, these are the major reasons that current ESUR guidelines strongly discourage the use of GBCA for radiographic examinations (Thomsen, 2002).

Due to the short-lived effect of GBCA injection in CT, this vascular enhancement is less cumbersome in clinical practice when combining contrast-enhanced CT and MRI examinations on the same day. One exception is that the kidneys will concentrate the gadolinium, so that the renal collecting systems, ureters, and bladder will show CT enhancement for a significant period.

*Combining CT and MRI: Effects of ICM on MRI studies*

In vitro experiments in MR Arthrography may serve as a model of these effects. Mixing of ICM with GBCA will lead to some shortening of the T1 (spin-lattice) relaxation time, and a more profound shortening of the T2 (spin-spin) relaxation time. This results in an increase in T1w signal and a decrease in T2w signal. The magnitude of the effect is greater for higher GBCA concentrations. The presence of ICM shifts the peak SI towards lower GBCA concentrations. Overall, in small joint spaces the enhancement was decreased (Andreisek, 2008; Choi, 2008; Ganguly, 2007; Kopka, 1994; Montgomery, 2002).

Similar effects can also be seen in routine MRI examinations, but to a lesser degree. The shortening effect on T1 and T2 times, with increase in T1w signal and a decrease in T2w signal, depends on the concentration of the ICM and on the side chains in the molecular structure of the specific ICM that is used (effect is for ioxithalamate > iotrolan > iopamidol > iodixanol, iohexol or iomeprol) (Hergan, 1995; Jinkins, 1992; Kopka, 1994; Morales, 2016). Very recently it was shown that adding an overdose of ICM to macrocyclic GBCA led to a significant increase in R1 relaxation and the combination was excreted more slowly, possibly because of the formation of chemical adducts between the lipophilic three-iodo-benzene rings of the ICM and the tetra-aza-cycle of the macrocyclic GBCA (DiGregorio, 2022). Increasing concentrations of ICM will also influence diffusion weighted imaging, with increased signal and decreased ADC values (Ogura, 2009), and on functional imaging with shortening of the T2* times used in BOLD MRI (Wang, 2014).

The effects of ICM in MRI can be longer-living and will be more disturbing on subsequent contrast-enhanced MRI.

## Zoeken en selecteren

For this chapter it was decided not to perform a systematic literature analysis, and therefore no search question with PICO was formulated.

Search and select (Methods)
The guideline authors decided to perform an explorative search. The explorative search was performed in the databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until

April 13th, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 441 hits.
Studies were selected based on the following criteria: any contrast medium (IBM, GBCA or other), study reported on pharmacokinetics or biodistribution parameters, and any study design (clinical, preclinical, in vitro etc.). The authors also added pharmacokinetics studies from their own database and articles found through cross-referencing.

No systematic literature analysis was performed. Instead, the authors made an overview of all available literature. A narrative literature analysis can be found below.

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

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# Analytische Interferentie van contrastmiddelen met klinische laboratoriumtesten

## Uitgangsvraag

Hoe kunnen contrastmiddelen (CM) interferentie geven op vaak toegepaste laboratorium testen?

1. Interferentie door jodiumhoudende CM
2. Interferentie door gadoliniumhoudende CM

## Aanbeveling

Bloedanalyse

Wees bewust dat een potentiële interferentie van CM op laboratoriumtesten bestaat, en dat dit cruciaal is om onnodige work-up van patiënten te voorkomen.

Zoals bij alle laboratoriumtesten moeten de resultaten worden geïnterpreteerd in relatie tot de medische geschiedenis en het klinische onderzoek van de patiënt.

Consulteer de laboratoriumarts wanneer er discrepanties zijn tussen de klinische presentatie en de uitslagen van laboratoriumtesten.

Voer bloedonderzoeken uit voordat toediening van CM plaatsvindt of stel bloedonderzoek uit voor niet-spoedeisende klinische laboratoriumtesten voor een periode van*:

- Tenminste 4 uur en optimaal 12 uur na toediening van CM bij patiënten met een normale nierfunctie (eGFR > 60 mL/min/1.73 $m^2$)
- Tenminste 16 uur en optimaal 48 uur na toediening van CM bij patiënten met een gereduceerde nierfunctie (eGFR 30-60 mL/min/1.73 $m^2$)
- Tenminste 60 uur en optimaal 168 uur na toediening van CM bij patiënten met een ernstig gereduceerde nierfunctie (eGFR < 30 mL/min/1.73 $m^2$)

*Zie ook 10.1 Meerdere onderzoeken met contrastmiddelen bij patiënten met normale of gereduceerde nierfunctie

Urine-analyse

Voer urineonderzoek uit voordat toediening van CM plaatsvindt of stel urineonderzoek uit voor niet-spoedeisende klinische laboratoriumtesten voor een periode van**:

- Tenminste 24 uur na toediening van CM bij patiënten met een normale nierfunctie (eGFR > 60 mL/min/1.73 $m^2$)
- Tenminste 48 uur na toediening van CM bij patiënten met een gereduceerde nierfunctie (eGFR 30-60 mL/min/1.73 $m^2$)
- Tenminste 168 uur na toediening van CM bij patiënten met een ernstig gereduceerde nierfunctie (eGFR

< 30 mL/min/1.73 $m^2$)

** Criteria zijn gebaseerd op bijna complete eliminatie van CM

## Overwegingen

### 1. Iodine-based contrast media interference with laboratory tests

The effect of iodine-based contrast media (ICM) on clinical assays has not been systematically studied extensively. Depending on method and ICM used, interference may be clinically relevant (Morcos, 2005). M-protein analysis is paramount in the diagnosis and monitoring of monoclonal gammopathy (Dimopoulos, 2021). Several studies report interference of ICM on the spectrophotometric detection of monoclonal protein analysis by capillary zone electrophoresis with spectrophotometric detection (CZE-UV) (Quirós, 2018). ICM absorb UV-light at a similar wavelength as the peptide bonds in m-proteins, thereby mimicking the presence of (M-)proteins in the commonly used CZE analysis with UV detection. In contrast, Capaldo and co-workers (Capaldo, 2021) demonstrated that the opposite may also occur, i.e., masking an M-protein peak. In the M-protein analysis by CZE- UV, a duplication in the beta-2 fraction which was at first assigned to ICM (iomeprol) interference and the beta-1 fraction did not display any M-protein peak. Further analysis demonstrated that the iomeprol peak should appear in the beta-1-fraction and not in the beta-2-fraction. After 6 days, a new urine sample demonstrated a m-protein in the beta-1- fraction, which was masked by the iomeprol interference.

Otnes and co-workers investigated in vitro the analytical interference of two specific ICM, iodixanol and iomeprol (Otnes, 2017). They reported in the high, but clinically relevant, concentration range of the ICMs, either a positive bias (colorimetric calcium assay) or a negative bias, i.e., colorimetric iron, magnesium, and zinc assay as well as in the direct potentiometric sodium assay. Other assays did not show any interference with both ICMs. In another study, Lin and co-workers (Lin, 2006) investigated the interference of ICM on two cardiac Troponin I immunoassays (Opus Magnum (Behring Diagnostics) and the Access (Beckman Coulter, Inc)) in patients undergoing coronary angiography. In two in-vivo and two in-vitro experiments, they demonstrated a clinically relevant interference of the ICM on the cardiac levels on the Opus system, especially in the samples obtained directly after the coronary angiography procedure. The interference was absent in the sample after 30 minutes from patients with normal kidney function and lasted longer than 30 min in patients with reduced kidney function. In contrast the Access did not show any interference in the in vivo experiments. In the same study, in vitro experiments of 12 different ICMs showed a similar interference on the Opus system for all ICMs and only one (Lipiodol) on the Access system. A similar interference by iohexol on endocrine immunoassays was observed by Loh and co-workers in in-vitro experiments (Loh, 2013). They reported that soon after contrast administration iohexol may affect follicle stimulating hormone (FSH), luteinizing hormone (LH), plasma renin activity (PRA) and thyrotropin (TSH) measurements by different manufacturers. The interference on immunoassays may be explained by either the presence of an unidentified antigenic site on the contrast medium molecule blocking or cross-reacting with antibodies, dilutional effects due to the high osmolar aspects of iohexol and/or, as described before, due to spectrophotometric aspects of the ICM, interfering with UV- detection.

Next to the photometric aspects of ICM, the higher refractive index of the ICMs interference may occur in urinary analysis, e.g., specific gravity measurement (Glasson, 2012; Oyaert, 2021; Strassinger, 2008).

Besides interference on laboratory testing, sample integrity and quality may be impacted (Lippi, 2014). Since, due to the presence of ICM in the blood, the density of blood is altered, thereby potentially influencing gel cell separator characteristics resulting in incorrect plasma or serum collection (Daves, 2012; Kaleta, 2012; Spiritus, 2003).

Table 10.2.1 shows commonly demonstrated ICM interference on clinical laboratory tests. Unfortunately, there are not many systematic studies addressing CM interference on clinical laboratory tests and recommendations (Stacul, 2018) rely mainly on CM elimination. ESUR for instance recommends performing blood and urine clinical tests prior to administration of the GBCA, to circumvent interference and incorrect assessment of the patient. Post-imaging non-emergency blood and urine analysis should be delayed until the CM concentration in blood and/or urine is not present anymore. In emergency testing, blood and urine analysis can be performed, though clinicians and laboratory specialists should be aware of potential interference of CM. As is with all laboratory tests, the results should be interpreted in relationship with the patient's medical history and clinical examination.

**Table 10.2.1 Clinical and/or analytical significant analyte interference of specific ICMs**

| **Iodine-based Contrast Media** | | | | |
|---|---|---|---|---|
| **Analyte** | **Method/technique** | **Name ICM** | **Observed Interference (bias)** | **Reference** |
| Albumin | Colorimetric assay | Iodixanol | ↑ | Otnes, 2017 |
| Aldosterone | Radioimmunoassay with I125-tracer | Iohexol | ↓ | Loh, 2013 |
| Bicarbonate | Enzymatic assay | Iomeprol, iodixanol | ↓ | Otnes, 2017 |
| Calcium | Colorimetric assay | Iomeprol, iodixanol | ↑ | Otnes, 2017 |
| Chloride | Ion selective electrode | Iohexol | ↓ | Sankaran, 2019 |
| Cortisol | Immunoassay with spectrophotometric detection | Iohexol | ↑ | Loh, 2013 |
| C-peptide | Immunoassay with spectrophotometric detection | Iohexol | ↓ | Loh, 2013 |
| Erythrocytes in urine | Fluorescence flow cytometry | Iomeprol | ↑ | Oyaert, 2021 |
| Follicle Stimulating Hormone | Immunoassay with spectrophotometric detection | Iohexol | ↓ | Loh, 2013 |

| | | | | |
|---|---|---|---|---|
| Insulin | Immunoassay with spectrophotometric detection | Iohexol | ↓ | Loh, 2013 |
| Iron | Colorimetric assay | Iodixanol | ↑ | Otnes, 2017 |
| LDH | Enzymatic assay | Iodixanol | ↓ | Otnes, 2017 |
| Leukocytes in urine | Fluorescence flow cytometry | Iomeprol | ↑ | Oyaert, 2021 |
| Luteinizing Hormone | Immunoassay with spectrophotometric detection | Iohexol | ↓ | Loh, 2013 |
| Magnesium | Colorimetric assay | Iomeprol | ↓ | Otnes, 2017 |
| M-proteins | CZE-UV | Iomeprol, iohexol, meglumine iotroxate, sodium meglumine amidotrizoate, Ioversol, Iopromide, Iobitridol, Iopamidol, Ioxitalamic acid, Ioversol | ↑, ↓ | Arranz-Pena, 2004; Capaldo, 2021; Vermeersch, 2006; |
| Potassium | Potentiometric assay | Iodixanol, Iomeprol | ↑ | Otnes, 2017 |
| Renin activity | Radioimmunoassay with I125-tracer | Iohexol | ↓ | Loh, 2013 |
| Sodium | Potentiometric assay, Ion selective electrode | Iometrol, iodixanol, iohexol | ↓ | Otnes, 2017; Sankaran, 2019 |
| Specific gravity in urine | Refractometry | Iomeprol, iohexol, iodixanol | ↑ | Giasson, 2012; Oyaert, 2021 |
| Thyroid Stimulating Hormone | Immunoassay with spectrophotometric detection | Iohexol | ↓ | Loh, 2013 |
| Troponin I | Immuno-enzymatic assay | 11 ICMs, a.o. Iopromide, ioversol, iohexol | ↑ | Lin, 2006 |
| Zinc | Colorimetric assay | Iodixanol | ↓ | Otnes, 2017 |

*N.B. Interference may be manufacturer/analyser specific. For detailed information see references.*

**2. Gadolinium-based contrast agent interference with laboratory tests**

Since the introduction of gadolinium-based contrast agents (GBCA) in 1983, these contrast agents have been used extensively. Several interferences on laboratory tests have been described, ranging from commonly used laboratory tests (Lippi, 2014) to more specialized laboratory tests (Day, 2019). One of the most reported

clinically relevant interferences is the interference of GBCAs, especially gadodiamide (Normann, 1995; Prince, 2003; Prince, 2004; Zhang, 2006) and gadoversetamide (Lin, 1999) on serum calcium measurement by specific colorimetric methods, irrespective of the molecular configuration of the CA (i.e., linear or cyclic and ionic or non-ionic) (Prince, 2003). Depending on the colorimetric method used the potential bias could be either absent, positive, or negative. In principle, other methods to measure calcium, e.g., Inductively Coupled plasma Mass Spectrometry (ICP-MS) does not demonstrate clinically relevant interference.

In an in-vitro study Proctor and co-workers (Proctor, 2004) investigated the analytical interference of four GBCAs on multiple analytes and multiple analysers. They demonstrated that depending on the specific GBCA a positive and negative analytical interference is observed, which is most prominent in Angiotensin Converting Enzyme (ACE), calcium, iron, total iron binding capacity (TIBC), magnesium and zinc. Mechanistically, all the affected analytes are either endogenous divalent cations or somehow use divalent cations in the reaction of the laboratory test. $Gd^{3+}$ can interact with the analyte of interest (e.g., transmetallation), thereby potentially interrupting the analytical process or in colorimetric assays by binding with the chromophore (Yan, 2014). In an in-vitro experiment, Otnes and co-workers demonstrated a similar interference by the GBCAs gadoxetate disodium, gadoterate meglumine, and gadobutrol on iron and zinc (negative bias) assays. Other 29 clinical tests did not display any clinically relevant interference by these GBCAs (Otnes, 2017).

In the field of trace elements and heavy metals, ICP-MS is the golden standard. Gd3+ may interfere also with this technique in multiple ways, i.e., space-charge effects, interference in the mass spectrometry analysis by double charged ions and polyatomic interference (Day, 2019). The latter can be circumvented by applying the correct analytical technique. In the study, Day and co-workers shared their experience with the clinical impact of GBCA interference in their clinical metal's laboratory. Especially in the analysis of selenium by ICP- MS is complicated by the presence of $^{156}Gd$ which may be doubly charged in the ionization process and therefore has a similar m/z ratio. Moreover, the presence of excess of Gd ions may interfere with the ionization process, suppressing ions of analytes, e.g., trace elements or (toxic) heavy metals and internal standards used.

It is worth noting that many studies report interference of gadodiamide and gadoversetamide on calcium assays but these GBCAs no longer available on the European market.

Table 10.2.2 shows commonly described GBCA interference on clinical laboratory tests. Assay interference by GBCAs can be contrast agent specific, analyte specific and method specific.

**Table 10.2.2 Clinical and/or analytical significant analyte interference of specific GBCA**

| Gadolinium Based Contrast Agents | | | | |
|---|---|---|---|---|
| **Analyte** | **Method/technique** | **Name GBCA** | **Observed interference (bias)** | **Reference** |
| ACE | Colorimetric enzymatic reaction | Gadodiamide, gadoversetamide | ↓ | Proctor, 2004 |
| Calcium | Several colorimetric assays | Gadodiamide, gadoversetamide | ↓ | Proctor, 2004; Yan, 2014 |
| Iron | Colorimetric assay | Gadodiamide, gadoversetamide, gadopentetate dimeglumine, gadoxetate disodium | ↓,↑ | Otnes, 2017; Proctor, 2004 |
| Magnesium | | Gadodiamide, gadoversetamide | ↓,↑ | Proctor, 2004 |
| Selenium | ICP-MS | Not specified | ↑ | Harrington, 2014; Ryan, 2014 |
| TIBC | Colorimetric assay | Gadodiamide, gadoversetamide | ↑ | Proctor, 2004 |
| Troponin I | Immuno-enzymatic assay | Gadopentetate dimeglumine | ↑ | Lin, 2006 |
| Zinc | Colorimetric assay | Gadodiamide, gadoversetamide, gadopentetate dimeglumine, gadoteridol, gadoxetate disodium | ↓ | Otnes, 2017; Proctor, 2004 |

*N.B. Interference may be manufacturer/analyser specific. For detailed information see references. Note: Gadodiamide and gadoversetamide are currently not on the market in the EU.*

**Recommendations**

*Recommendations are similar to the recommendations in the ESUR guideline version 10.0 (ESUR, 2018; Morcos, 2005) and based on pharmacokinetics and elimination recommendations in Chapter 10.1 Safe time intervals between contrast-enhanced studies.*

Blood Analysis

Be aware that the potential interference of contrast media on laboratory tests is crucial to prevent adverse patient work-up. As with all laboratory tests, the results should be
interpreted in relationship with the patient's medical history and clinical examination.

Consult the laboratory specialist if there are any discrepancies between clinical presentation and laboratory tests.

Perform clinical laboratory testing prior to administrating contrast media or delay blood collection for non-emergency clinical laboratory testing* for:

- At least 4 hours and optimally 12 hours after administration of the contrast medium in patients with normal kidney function (eGFR > 60 mL/min/1.73 $m^2$)
- At least 16 hours and optimally 48 hours after administration of the contrast medium in patients with reduced kidney function (eGFR 30-60 mL/min/1.73 $m^2$)
- At least 60 hours and optimally 168 hours after administration of the contrast medium in patients with reduced kidney function (eGFR < 30 mL/min/1.73 $m^2$)

Urine Analysis

Perform urine clinical laboratory tests prior to contrast media administration. Another option is to delay urine collection for at least**:

- 24 hours after administration of the contrast medium in patients with normal kidney function (eGFR > 60 mL/min/1.73 $m^2$)
- 48 hours after administration of the contrast medium in patients with reduced kidney function (eGFR 30-60 mL/min/1.73 $m^2$)
- 168 hours after administration of the contrast medium in patients with reduced kidney function (eGFR < 30 mL/min/1.73 $m^2$)

## Onderbouwing

### Achtergrond

Radiological imaging with (or without) contrast media (CM) and laboratory tests are commonly used complimentary tools in the diagnosis and monitoring of patients. In terms of efficient patient work-up, these tools are often planned together. Though most clinicians are not aware, several studies have reported interference of iodine-based contrast media (ICM) and gadolinium-based contrast agents (GBCA) with several clinical laboratory tests.

Awareness of these interferences is important since they may pose a potential threat by misdiagnosing and/or incorrect monitoring of patients, denying or delaying their treatment or initiating/continuing undesirable treatment (Doorenbos, 2003). These clinically relevant interferences are specific for the contrast media administered as well as for the specific technique/method used for the analysis of the biomarker (Otnes,

2017).

N.B. (Patho)physiological responses of the body, represented by specific biomarkers, e.g., thyroid function (Bednarczuk, 2021), coagulation status (Aspelin, 2006; Lukasiewicz, 2012), due to the administration of contrast agents are outside of the scope of this chapter.

## Verantwoording

Laatst beoordeeld : 28-11-2022

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

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# Andere veiligheidsmaatregelen

## Verantwoording

Laatst beoordeeld :

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

# Contrastmiddeltoediening door middel van power injectors

## Uitgangsvraag

Hoe kunnen centraal veneuze katheters (CVC), hemodialyse katheters (HC), perifeer ingebrachte centrale katheters (PICC), en totally implantable venous access devices (TIVAD, poorten) veilig worden gebruikt voor het toediening van intraveneuze contrastmiddelen (CM), in het bijzonder bij het gebruik van power injectors en hogere injectiesnelheden voor het verkrijgen van afbeeldingen van hoge kwaliteit?

## Aanbeveling

Opmerking: Hoge beeldkwaliteit is meestal nodig bij laag-contrast situaties, zoals bij (stagerings)onderzoeken in de hersenen, in het hoofd-hals gebied of bij hepatobiliaire, genito-urinaire of colorectale onderzoeken in het abdomen. Lagere beeldkwaliteit kan acceptabel zijn in hoog-contrast situaties zoals bij pulmonaire of musculoskeletale beeldvorming, of bij de follow-up van lymfeklieren (bv. lymfomen, testiscarcinoom).

| |
|---|
| Gebruik een power-injector en perifere veneuze katheter voor intraveneuze CM toediening om de beste kwaliteit van beeldvorming na contrasttoediening te verkrijgen, vooral in laag-contrast situaties (zie Opmerking). |
| Controleer voor én na CM toediening met een power injector de positie en doorgankelijkheid van een CVC, TIVAD of PICC lijn wanneer een perifere veneuze katheter niet beschikbaar is. |
| Power-injecteerbare centraal veneuze katheters kunnen veilig worden gebruikt voor de toediening van CM met een power-injector wanneer de meeste recente aanbevelingen van de fabrikant van de katheter worden opgevolgd. |
| Power-injecteerbare hemodialyse katheters kunnen veilig worden gebruikt voor de toediening van CM met een power-injector wanneer de meest recente aanbevelingen van de fabrikant van de katheter worden opgevolgd. |
| Wanneer CM wordt geïnjecteerd met een power-injector bij patiënten met een PICC lijn of TIVADs waarvan de kathertertip boven de tracheobronchiale hoek ligt is er risico op migratie van de kathetertip van deze lijnen. Controleer daarom bij een PICC of TIVAD met kathetertip boven de tracheobronchiale hoek de positie van de kathetertip met een röntgenfoto, CT instelopname, of doorlichting voor én na CM toediening met een power injector. |
| Wanneer een voor power-injectie geschikte CVC, HC, PICC of TIVAD wordt gebruikt voor CM toediening met een power-injector, controleer dan of de katheter nog open is door handmatig te spoelen met 20 ml fysiologisch zout na de injectie<br><br>Wanneer een voor power-injectie geschikte HC wordt gebruik voor CM toediening met een power injector, moet een patient-specifieke oplossing om de catheter af te sluiten direct na injectie worden aangelegd door een gecertifceerde dialyse verpleegkundige. |
| Zie Appendix 1 voor aanbevelingen over stroomsnelheden en injectiedruk voor een groot aantal commercieel beschikbare CVC's, HC's, PICC's en TIVAD's in Nederland. |

## Overwegingen

A patent intravenous access site is needed for the administration of intravenous contrast through power injection in order to obtain high quality contrast enhanced or angiographic images. Local hospital guidelines should be available to guide the proper and safe administration technique for the applied contrast medium, but these a frequently limited to peripheral venous injection only. Possible complications of IV contrast injection are: contrast medium extravasation, air embolism, catheter rupture, catheter weakening, and loss of catheter patency.

With the use of power injectors, injection pressure is also a function of the injected CM. In general, the use of lower concentrations of the CM, low viscosity of the CM, and high temperature of CM are beneficial to keep injection pressures as low as possible (Macha, 2009; Kok, 2014). There are only a limited number of studies that compare the safety and efficacy of different venous access sites. No difference is reported in patency between CVCs or peripheral venous access catheters, however there seems to be a difference in the level of the contrast enhancement of large vessels, which affects the image quality in favour of a peripheral venous access. A short peripheral IV catheter in the antecubital or forearm is therefore the preferred route for contrast administration. However other routes may be needed and each is considered separately below.

Central Venous Catheters (CVC)

In the comparative studies, there is no difference in reported complications in terms of patency related to the contrast medium power injection compared to peripheral venous access sites. However, image quality is limited compared to peripheral venous access sites.

Herts (Herts, 1996) also performed an in vitro study with 10F Hickman and Leonard CVCs, and found that CM, flow rate and catheter type were main determinants of peak injection pressures. The peak injection pressures remained well within manufacturer limits of 25 psi (175 kPa).

In an in vitro study with a 3-lumen 16G (4.9F) Arrow CVC, a significant safety margin was shown for CVCs, with bursting pressures depending on catheter dwell time, 262 PSI for new and 213 PSI for used catheters. Lowest flow rate associated with bursting was 9 ml/s. Ruptures occurred always *outside* the patient (Macha, 2009).

Similar high bursting pressures were seen in other studies. A study using 3-lumen 16G CVCs showed pressure to be above 175 PSI, whereas high flow injections 4,5 to 7,0 ml/s were associated with injection pressures of 48 to 81 PSI (Beckingham, 2017). An older study found no catheter failures at flow rates of 5 to 25ml/s with an even higher bursting pressure of 920 psi (Zamos, 2007).

To help prevent the rupture of vascular access devices when they are used with power injectors, the FDA long ago has already issued recommendations (FDA, 2004).

Users of central vascular access devices should:

1. Check the labelling of each vascular access device for its maximum pressure and flow rate. If none is provided, assume device is NOT intended for power injection and do not use.
2. Know the pressure limit setting for your power injector and how to adjust it.
3. Ensure that the pressure limit set for the power injector does not exceed the maximum labelled pressure for the vascular access device(s).

Haemodialysis Catheters (HC)

There are no patient controlled studies available that compare the usability and safety of dialysis catheters for IV contrast administration through power injection versus peripheral IV catheters or central venous catheters. However, haemodialysis catheters have larger diameters than other venous catheters. An in vitro study on

cuffed and non-cuffed catheters for haemodialysis showed that pressure inside the catheters (14,0 ± 3,3 PSI) was 23x lower than the pressures indicated by the power injectors (338 ± 8,7 PSI). It is believed that the high pressures in the injector are mainly caused by the long, small calibre connection tubing that connects the injector to the HC (Hollander, 2012). Therefore, their use for power injection should be safe when adhering to the recommendations of the manufacturer. Adjustments to the scan protocol may be needed to preserve optimal image quality. Especially in chronic dialysis patients with poor vascular conditions vein preservation has a high priority.

Peripherally inserted catheters (PICC)
Spontaneous migration of PICCs is a known complication in 1.5 to 3% with multifactorial aetiology (Seckold, 2015). Multiple other case series have confirmed that the catheter tip of power-injectable PICCs can migrate due to the power injection during CT (Lambeth, 2012; Craigie, 2018). Tubing ruptures during power injection are reported when there is a mechanical obstruction such as a clamped port or kinking of the line. Silicone catheters are have higher failure rates than polyurethane catheters and are unsuitable for power injection (Salis, 2004). Strict protocols are recommended to check its position via CT scout/scanogram radiograph before and after power injection during CT, and to check patency of the catheter after CM injection.

Totally Implantable Venous Access Devices (TIVAD)
A retrospective analysis of TIVADs with silicone catheters showed a 3.4% rate of complications (Busch 2012; Busch, 2017). Newer power-injectable TIVADs have a high patient satisfaction rate and with no device failures during power injections (Alexander, 2012; Chang, 2013).
There are no data on catheter tip migration in TIVADs, mainly because they are tunneled catheters inserted surgically with a deep position of the catheter tip. Theoretically, for devices with high positions of the catheter tip, the same risks for migration as in PICCs would exist.
The GAVeCeLT group formulated already in 2011 recommendations to prevent complications with TIVADs and recommends only using systems specifically suitable for power injection with adequate check of catheter position (Bonciarelli, 2011.
A Canadian study on CT image quality showed that contrast injection via a CVC or port system has equivalent image quality when compared to conventional peripheral intravenous injection technique. (Haggag, 2016)

## Onderbouwing

## Achtergrond

Power injection of contrast through CVCs, HCs, PICCs, and TIVADs holds a risk for device failure and secondary contrast extravasation. The exact method how to "power-inject" with respect to applied pressure limitations remains part of local practice guidelines combined with the central catheter line manufacturer's instructions.

## Conclusies / Summary of Findings

| | |
|---|---|
| **Very Low GRADE** | The frequency of complications following contrast injection via CVCs, without safety protocols, varies from 0,6% to 15,4% across studies.<br><br>*Sources: (Coyle, 2004; Goltz, 2011; Herts, 2001; Lozano, 2012; Morden, 2014)* |

| | |
|---|---|
| **Very Low GRADE** | It seems that contrast injections via CVCs are a safe alternative to peripheral injection if safety protocols are followed.<br><br>*Sources: (Coyle, 2004; Goltz, 2011; Herts, 2001; Lozano, 2012; Morden, 2014)* |
| **Very Low GRADE** | There were no complications reported following contrast injection via CVCs when strict safety protocols were implemented.<br><br>*Sources: (Macht, 2012 and Sanelli, 2004)* |
| **Very Low GRADE** | Safety protocols are warranted when contrast injections are performed via central venous catheters, and should include aspirating blood before injecting contrast media, localizing the CVC before and after injection, making sure no kinking of the CVC and attached lines occurs, using sterile syringes, and making sure the CVC is patent after scanning.<br><br>*Sources: (Macht, 2012 and Sanelli, 2004)* |
| **Very Low GRADE** | It is unknown whether contrast injections via CVCs result in successful contrast media examination as quality of scans varies among studies.<br><br>*Sources: (Coyle, 2004; Goltz, 2011 and Herts, 2001)* |
| **Very low. GRADE** | It seems that power injectable PICCs positioned in the proximal SVC (cephalic to tracheobronchial angle) before contrast administration had a higher risk of displacement compared to catheters positioned in the distal SVC (caudal to tracheobronchial angle) before contrast administration.<br><br>*Source: (Lozano, 2012)* |

### Samenvatting literatuur

Buijs (2017) described a systematic literature review on the efficacy of contrast injection via central venous catheters for contrast enhanced computed tomography. A search query was built by linking two content areas: 'central catheter' and 'contrast enhanced' with relevant synonyms for both areas. Publications were selected, describing original research on the use of CVCs for contrast administration for CT-scans focusing on safety, efficacy, and complications. Exclusion criteria included: no full-text available, publication not written in English or Dutch, review articles, case reports, and studies focusing on the use of CVCs in paediatrics. Two independent assessors screened titles and abstracts for full-text selection. Studies were classified as having low risk of bias if they satisfied all criteria and high risk of bias if they satisfied less than three criteria. The remaining studies were classified as having a moderate risk of bias. (See risk of bias assessment). Frequencies of complications were extracted from the selected studies were tabulated and presented as percentages. Data on quality of images was extracted where applicable. Twenty-three articles were considered eligible for answering the research question after selection based on title and abstract. Seventeen articles were excluded during full text screening. During cross-referencing, one study was included missed by the initial search (Carlson, 1992; Goltz, 2011). Eventually, eight studies were included for critical appraisal (Coyle, 2004; Goltz, 2011; Herts, 2001; Lozano, 2012; Macht, 2012; Morden, 2014; Sanelli, 2004). Carlson (1992) evaluated the

system pressure in thirteen patients with a Port-A-Cath. The pressure measurement was not standardized: five patients' injection pressures were measured with a pressure gauge that was placed in-line during injection and eight patients' injection pressures were not. The lack of standardization and limited relevance led to the exclusion of this study. Finally, seven studies were included for further analysis (Coyle, 2004; Goltz, 2011; Herts, 2001; Lozano, 2012; Macht, 2012; Morden, 2014; Sanelli, 2004). Table 11.1 presents study characteristics and main outcome measures on safety and image quality. Individual outcome measures among studies on safety and efficacy are described separately.

**Table 11.1 Study characteristics and main findings for complications and image quality**

Results

*1. Complications following contrast injection via central catheters*

*Central Venous Catheters (CVC)*

Herts (2001) randomized 225 patients, after reassignment because of inability to obtain access, in a central venous access group (n= 174) and a peripheral venous access group (n= 51). No significant differences in early, delayed, and late complications were found. In the central venous access group, one (1/174; 0.6%) patient reported that her device was no longer patent, while being successfully used for chemotherapy after contrast injection. In one (1/174; 0.6%) patient an infection was reported. Macht (2012) and Sanelli (2004) implemented a strict safety protocol, in which they verified the correct position of the CVC in the superior vena cava (SVC) on scout view before contrast injection, checked for adequate blood return, and checked the patency of the catheter afterwards. They did not report complications relating to the injection using the CVC.

*Peripherally inserted catheters (PICC)*

Coyle (2004) found two (2/110; 1.8%) externally ruptured PICCs while injected at a rate of 2 mL/sec. Ruptures were caused by mechanic obstructions; i.e. one of the ruptured PICCs was clamped, the other kinked at the venous entry site. Another PICC ballooned without rupturing and further injected was stopped.

Lozano (2012) evaluated the frequency of displacement of power-injectable PICC (PI-PICC) after contrast injection. Correct catheter position was defined as cephalic to or caudal to the right tracheobronchial angle. A total of 12/78 (15.4%) PI-PICC tips changed in position after injection of contrast medium. Seven displaced toward the brachiocephalic veins. They found that PI-PICCs positioned in the proximal SVC (cephalic to tracheobronchial angle) before contrast administration had a higher risk of displacement compared to catheters positioned in the distal SVC (caudal to tracheobronchial angle) before contrast administration (5/8 (62.5%) versus 7/69 (10.1%)). Distal location in the SVC decreased this risk by 89% (RR= 0.11; 95%CI= (0,026; 0,487); p= 0.006).

Morden (2014) evaluated a rate increase technique of the saline flush after contrast injection via power-injectable PICCs (PI-PICC), in which they started with a saline flush at 2 mL/s and progressively increased to the rate of contrast injection. With this technique, they found a lower percentage of PI-PICC tip displacement (20/243 (8.2%) without rate increase technique versus. 3/138 (2.2%) with rate increase technique).

*Totally Implantable Venous Access Devices (TIVAD)*

Goltz (2011) evaluated power injections in 141 patients with totally implantable venous access ports (TIVADs)

in their forearm. One (1/141; 0.7%) TIVAD catheter tip was dislocated into the brachiocephalic vein and revealed a catheter rupture during an interventional retrieval attempt. Three (3/141; 2.1%) catheter tips were suspected of a systemic infection within four weeks.

*2. Contrast enhancement and image quality*
*Central Venous Catheters (CVC)*
In Herts (2001), two reviewers who were blinded for route of injection measured the enhancement of the large vessels. The level of enhancement of the thoracic aorta, pulmonary artery, and liver vasculature was significantly less dense in the central venous access group compared to the peripheral venous access group. No significant difference was seen in the enhancement of the abdominal aorta.

*Totally Implantable Venous Access Devices (TIVAD)*
In Coyle (2004) CT images were assessed subjectively by the radiologist supervising the CT examination, which resulted in categorizing the quality of CT images as average in 81/110 (74%) of cases and above average in 23/110 (21%) of cases.

Goltz (2011) found a significantly lower arterial contrast density in patients with TIVADs compared with classic peripheral cannula, resulting in limited image quality. In 31/44 (70.4%) examinations, manual initialization was necessary, while initial arterial bolus tracking was performed, because the trigger threshold had not been reached in time. This might be the result of the lower flow rate of 1.5 mL/s through TIVADs. Triggering with automatic scan initiation resulted in significantly higher contrast in the aorta compared to manual scan initiation (163 HU versus 144 HU, p =0.039).

Quality of evidence
The quality of certainty of evidence was graded as very low due to high risk of bias (see Table Risk of Bias assessment, downgraded by one point) and low number of patients (imprecision, downgraded by two points) and lack of studies where a control group was present.

## Zoeken en selecteren

A systematic literature analysis was performed to answer the research question: How can central venous catheters (CVC), haemodialysis catheters (HC), peripherally inserted central catheters (PICC), and totally implantable venous access devices (TIVAD) be safely used for the administration of intravenous contrast agents, particularly using power injectors and higher injection rates for obtaining high-quality images?

**P** (Patient): Patients with central venous catheters (CVCs) or Peripheral inserted central catheters (PICCs) and an indication for administration of iodine-based contrast for performing computed tomography examinations.
**I** (Intervention): Non-tunneled central venous catheters (CVCs), tunneled CVCs, implantable ports, peripherally inserted central catheters (PICC).
**C** (Comparison): Normal Venflon, normal peripheral infusion.
**O** (Outcomes): Failure contrast media examination, contrast extravasation, failure of examination, damaged CVCs or PICCs, complication rates, device failure, and device dwell times.

Relevance of outcome measures

The working group considered the outcomes failure of contrast media examination, complication rates (damaged CVCs or PICCs, contrast media extravasation) critical measures and outcome for the decision making process. The working group did not define criteria for outcomes a priori, but used the outcomes as defined in the studies.

Methods
The databases Medline (OVID), Embase and the Cochrane Library were searched from 1st of January 1996 to March 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). A systematic literature search was conducted at May 16th 2018.

The literature search produced 97 hits: 2 SR, 13 RCTs and 13 OBS and 68 mixed designs. Based on title and abstract a total of 18 studies were selected. After examination of full text 0 articles were selected. Since there are no direct comparisons on the safety or efficacy of contrast injections via central venous catheters or peripheral inserted central catheters (PICCs) versus normal infusion, literature has been described in a descriptive manner. The SR of Buijs, 2017 was selected and covers the literature on efficacy and safety of contrast injection via central venous catheters for contrast enhanced computed tomography until September 10th 2016. This study was used as key article for the literature review. Studies published after September 10th 2016, on efficacy and safety of contrast injection via central venous catheters or peripheral inserted central catheters were added.

## Verantwoording

Laatst beoordeeld : 24-06-2020

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

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# Optimale behandeling van contrastmiddel-extravasatie

## Uitgangsvraag

Wat is de optimale behandeling voor contrastmiddel(CM)-extravasatie?

## Aanbeveling

| |
|---|
| Overweeg de volgende behandelingsopties voor extravasatie met CM:<br><br>• Probeer het extravasale CM via een ingebrachte naald op te zuigen.<br>• Markeer het getroffen gebied.<br>• Gebruik kompressen voor het verlichten van pijn op de injectieplaats.<br>• Gebruik pijnstillers.<br>• Plaats de getroffen extremiteit boven het niveau van het hart. |
| Documenteer de contrast-extravasatie en behandeling in het elektronisch patiëntendossier (volume, concentratie, oppervlakte, klinische bevindingen). |
| Geef de patiënt duidelijke instructies wanneer aanvullende medische zorg moet worden gezocht:<br><br>• Verergering van de symptomen.<br>• Huidulceratie.<br>• Ontwikkeling van eventuele neurologische of circulatoire symptomen, inclusief paresthesieën.<br><br>Geef de patiënt schriftelijke informatie mee. |
| In geval van ernstige extravasatieschade:<br><br>• Consulteer een plastisch chirurg.<br>• Breng de verwijzend arts op de hoogte. |

## Overwegingen

The working group has based this protocol on expert opinions and international guidelines.
At the end of the recommendations suggestions for further reading are given.

Extravasations and injuries
One or more of the following signs or symptoms can develop: progressive swelling or pain, altered tissue perfusion as evidenced by decreased capillary refill at any time after the extravasation has occurred, change in sensation in the affected limb, and skin ulceration or blistering. It is important to note that initial symptoms of a compartment syndrome may be relatively mild (such as limited to the development of focal paraesthesia).

Most extravasations result in minimal swelling or erythema, with no long-term sequelae.

Few extravasations result in significant tissue damage, i.e. severe skin necrosis and ulceration. Compartment syndrome may be seen associated with extravasation of large volumes and after extravasation of relatively small volumes in less capacious areas.
Extravasation can occur during hand or power injection.

The risk of extravasation is much less with GBCA injections.

Risk factors
*Location of extravasation:*
Less capacious areas (such as over the ventral or dorsal surfaces of the wrist) – higher risk
More capacious areas (such as upper arm) – lower risk

*Volume of extravasation:*
Large volume of contrast medium – higher risk

*Inability to communicate:*
Infants, young children, and unconscious and debilitated patients

Management

- Recognition of the extravasation, stop infusion of contrast media immediately.
- Try to aspirate the extravasated contrast medium through the inserted needle.
- Mark off affected area.
- Consultation of a radiologist.
- Surgical consultation (plastic surgeon) should be obtained whenever there is concern for a severe injury. Alternative: consultation of a physician in the emergency department.
- Clear instructions should be given to the patient to be aware of alarming symptoms.
- Appropriate patient information leaflets should be available. One should consider having these available in multiple languages.
- Appointments for follow up, if necessary.
- The referring physician should be notified.
- Record contrast extravasation and treatment in patient record (name, volume, concentration, area, clinical findings).
- Record names of all professionals involved in the patient management in patient record.
- Report contrast extravasation as a complication in the local reporting system.

Treatment
*Non-severe extravasation injury:*

- Use of cold of warm compresses, helpful for relieving pain at the injection site.
- Use of cold compresses, mainly helpful for relieving pain at the injection site.
- Use of warm compresses, helpful in improving absorption of the extravasation as well as in improving blood flow, particularly distal to the site.
- Use of pain medication (analgesics).

- Elevation of the affected extremity above the level of the heart to decrease capillary hydrostatic pressure and thereby promote resorption of extravasated fluid is recommended.
- Clear instructions should be given to the patient to seek additional medical care, should there be any worsening of symptoms, skin ulceration, or the development of any neurologic or circulatory symptoms, including paraesthesias.

*Severe extravasation injury:*

- Surgical consultation (plastic surgeon).
- Clear instructions should be given to the patient about the follow-up.

## Onderbouwing

### Achtergrond

Extravasation of intravascular (intravenous or intra-arterial) injected contrast (hand or power injection) is a well-recognized complication of contrast enhanced imaging studies (CT and MRI and US), angiography and interventions. Currently the clinical consequences and most optimal management is a matter of debate.

### Samenvatting literatuur

Not applicable. There were no studies investigating the research question.

### Zoeken en selecteren

To answer our clinical question a systematic literature analysis was performed.

**P** (Patient): Patients with extravasation after intravascular contrast Administration.
**I** (Intervention): Contrast aspiration, cooling of area of contrast extravasation, fasciotomy, necrotectomie, dilution, flushing with sterile water, application of ice, anti-inflammatory agents, corticosteroid, removal catheter, elevation of the affected limb / extremity, cold compresses, Plastic Surgery Review, monitoring the patient, surgical consultation.
**C** (Comparison): Conservative treatment or comparison of interventions above.
**O** (Outcomes): Rhabdomyolysis, tissue necrosis, long term injury / disability, compartment syndrome, pain, swelling and ulceration.

Relevant outcome measures
The working group considered compartment syndrome, tissue necrosis, and permanent or long-term injury or disability critical outcome measures for the decision making process, and location and volume of extravasation, pain, swelling, ulceration important outcomes for the decision making process.

Methods
The databases Medline (OVID), Embase and the Cochrane Library were searched from 1st of January 1996 to 7th of February 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS).

The literature search procured 480 hits: 1 SR, 41 RCTs and 438 OBS. Based on title and abstract a total of 22 studies were selected. After examination of full text a total of all studies were excluded and 0 studies definitely included in the literature summary.

## Verantwoording

Laatst beoordeeld : 24-06-2020

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

## Referenties

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# Contrast bij kinderen

De module 'Contrast bij kinderen' bestaat uit de volgende submodules:

- Hydratie strategieën bij kinderen
- Risicostratificatie bij kinderen
- Profylactische maatregelen om hypersensitiviteitsreacties na CM te voorkomen bij kinderen
- Behandeling van acute hypersensitiviteitsreacties na CM bij kinderen
- Monitoren van schildklierfunctie na het gebruik van jodiumhoudend contrastmiddel bij kinderen

## Verantwoording

Laatst beoordeeld : 01-12-2024

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

# Risk Stratification in the Prevention of PC-AKI

## Uitgangsvraag

Hoe dienen kinderen die verhoogd risico lopen op post-contrast acuut nierletsel (PC-AKI) te worden geïdentificeerd?

## Aanbeveling

Bepaal niet routinematig de nierfunctie bij gezonde kinderen die niet tot een risicopopulatie behoren.

Bepaal de nierfunctie (eGFR met behulp van de gemodificeerde Schwartz formule) voorafgaand aan het onderzoek met intraveneuze jodiumhoudende contrastmiddelen:

Bij kinderen met bekende nierziekte of nierfunctie stoornis
EN
Bij kinderen die tot een veronderstelde hoog risico groep voor PC-AKI behoren:

- Doorgemaakte nierziekte,
- Voorgeschiedenis van AKI,
- Congenital anomalies of the kidney and urinary tract (CAKUT),
- Voorgeschiedenis van Prematuriteit < 32 weken,
- Trisomie 21,
- Gebruik van nefrotoxische en renale perfusie beïnvloedende medicatie (ACEi, ARB (angiotensine receptor blokker), NSAIDs),
- Hypovolemie / bedreigde circulatie (bijvoorbeeld sepsis/ shock),
- Diabetes mellitus.

Wees in deze verhoogd risico populatie alert op nierfunctieproblemen en bepaal de nierfunctie (eGFR). Bij een stabiele kliniek is een bepaling tot 3 maanden voor het beeldvormend onderzoek geldig.

*Afspraken na beeldvorming*
Bereken de eGFR met behulp van de modified Schwarz formule: lengte (cm) x 36.5 / serum kreatinine (micromol/L) binnen 2 tot 7 dagen na intravasculaire jodiumhoudende CM-toediening bij elke patiënt met eGFR < 30 voor het onderzoek.

Indien er PC-AKI wordt gediagnostiseerd (volgens Kidney Disease Improving Global Outcomes criteria), vervolg de patiënt tot normalisatie van serum creatinine naar baseline en consulteer een kindernefroloog.

Gemodificeerde Schwartz formule: lengte (cm) x 36.5 / serum creatinine (micromol/L).
In kinderen met een lage spiermassa (bijvoorbeeld eetstoornis of cerebrale parese) kan de uitkomst van de formule incorrect zijn en dient overlegd te worden met een kinderarts/nefroloog.

## Overwegingen

Pros and cons of the intervention and quality of the evidence

The guideline development group conducted a systematic review of the increased risk for developing PC-AKI or complications related to PC-AKI after contrast exposure in children with prematurity, trisomy 21, diabetes mellitus, congenital anomalies of the kidney and urinary tract (CAKUT), renovascular medication or nephrotoxic medication. One article (Cantais, 2016) examined risk factors for developing PC-AKI. However, the evidence was of too low quality (very low GRADE) to draw a conclusion. No articles describing complications of PC-AKI met the inclusion criteria. Therefore, no conclusions could be drawn about the effects of these risk factors on the development of PC-AKI and complications related to PC-AKI (hospitalization, dialysis). A knowledge gap exists on this topic.

Multiple studies did not meet the inclusion criteria. Most of these studies were excluded based on wrong design, comparing contrast exposure to non-contrast exposure, where our PICO is aimed at identifying risk factors in contrast exposed groups only. These studies report low incidences of PC-AKI. McDonald (2018) published a cohort study on postcontrast acute kidney injury in pediatric patients, reporting a low rate of contrast associated AKI (3,3%) with no observed difference between contrast and noncontrast groups following propensity score analysis in a small sample with low rates of PC-AKI. Gilligan (2020) published similar results (PC-AKI 2.4%) in a cohort study in hospitalized children using propensity score analysis with no noticeable difference between exposed and non-exposed children in a small sample with low rates of PC-AKI. Calle-Toro (2022) published a retrospective cohort study in children undergoing CT scans with or without contrast media. They reported a PC-AKI incidence of 1.4% after contrast exposure, showing a difference in risk between contrast exposed and non-contrast exposed groups only in children with an eGFR < 60 prior to imaging.

The quality of the evidence from the systematic literature search is too low to draw a conclusion, the recommendations in this national guideline are based mainly on the guideline for PC-AKI risk stratification and stratification tools in adults (NVVR, 2017) when applicable. The low reported PC-AKI incidence in children in combination with the low prevalence of kidney disease in children however requires a different approach then mentioned in the guideline for adults. Based on expert opinion we describe the main differences below.

The vast majority of children that are scheduled for IV contrast-enhanced studies have no medical history, (past) use of nephrotoxic medication, or hypovolemia. This patient group can safely be scheduled for imaging without renal function testing and/or prehydration strategies.

The minority of children that are scheduled for studies with IV contrast media with known renal disease (including Congenital Anomalies of the Kidney and Urinary Tract or CAKUT) OR a medical history associated with an elevated risk of renal disease, including prematurity and use of renovascular or nephrotoxic medication, should have renal function tests performed (eGFR calculated using serum creatinine (in micromol/L) and patients height (in cm). Also euvolemia / adequate circulation should be guaranteed prior to imaging. In case of impaired renal function, prehydration strategies should be performed. An eGFR based on a serum creatinine sample within the last 3 months before imaging is considered valid, when the child is well appearing, in a stable condition and with no recent changes in his/her medical condition and medication. This is based on common practice in the absence of relevant articles/studies on this topic, in line with similar recommendations in, for example, the ESUR guidelines on contrast agents.

Patient (and their caretakers) values and preferences
Patients, parents/caretakers, and health care professionals like to make decisions based on the best available evidence. A similar case should get equal advice/treatment.
This guideline defines a patient group with an increased risk of PC-AKI. Patients at increased risk and their caretakers should be informed about the options available to them and together with their physician decide on risk reducing measures and alternative imaging modalities. The exact options will depend on many different factors such as type of examination and reason for performing a scan.
This guideline helps in identifying a population with an elevated risk, thereby reducing the chance of unnecessary tests and interventions.

Costs
Cases of PC-AKI are associated with additional healthcare costs both in the short and long term. Currently physicians are likely to be very careful in children and thus order additional diagnostic tests and interventions. The recommendations in this guideline can prevent unnecessary diagnostic tests and interventions, while simultaneously preventing unnecessary incidents of PC-AKI.

Acceptability, feasibility and implementation
The guideline development group does not anticipate any acceptance issues. The recommendations in the current guideline address longstanding uncertainty about the need for diagnostic testing and interventions. Therefore, it will contribute to a more unified and equal approach in children.

Rationale of the recommendation: weighing arguments for and against the interventions
We present a simple and uniform strategy to identify children at increased risk of developing PC-AKI. Children with known kidney disease are at risk and require renal function monitoring in the form of serum creatinine up to three months after contrast administration. We also identify an increased risk population where kidney problems may arise, and serum creatinine should be measured to determine renal function. This strategy should enable us to limit testing to a well-defined subgroup of patients, preventing unnecessary testing and costs. Since there are limited studies in children, the strategy is based mainly on evidence in adult populations as described in the guideline for PC-AKI risk stratification and stratification tools in adults (NVVR, 2017), supplemented by expert opinion to incorporate important difference in children. For instance, the lower prevalence of kidney disease led to no further action for children with no medical history, (past) use of nephrotoxic medication or hypovolemia. Based on the adult guideline we recommend testing for renal impairment prior to imaging. Based on expert opinion we limit this testing to a well-defined population at risk for renal impairment.

## Onderbouwing

## Achtergrond

Intravascular iodine-based contrast media could lead to PC-AKI in certain cases, especially when renal function is already impaired. At the moment there is no routine screening for impaired renal function in children exposed to intravenous contrast media as part of diagnostic or therapeutic imaging (for instance by measurement of serum creatinine or determination of Glomerular Filtration Rate or eGFR).
There are certain risk factors that may indicate renal dysfunction that worsens after administration of

intravenous contrast media. These risk factors include children with Down syndrome (trisomy 21), diabetes mellitus, prematurity or congenital anomalies of the kidney and urinary tract (CAKUT) as well as the use of renovascular or nephrotoxic medication. It is unclear whether screening for impaired renal function is necessary in children at increased risk of renal dysfunction.

## Conclusies / Summary of Findings

| | |
|---|---|
| **Very low GRADE** | The evidence is very uncertain about the identification of risk factors for PC-AKI in children (<18 years of age) undergoing radiological examinations with intravascular iodine-based contrast media.<br>*Source: Cantais, 2016* |

| | |
|---|---|
| **- GRADE** | No evidence was found regarding risk factors for complications of PC-AKI in children (<18 years of age) undergoing radiological examinations with intravascular iodine-based contrast media. |

## Samenvatting literatuur

Description of studies

Cantais (2016) published a retrospective chart review study of contrast-induced acute kidney injury (CI-AKI) incidence, risk factors and impact in paediatric patients (<16 years). CI-AKI is a specific term used to describe a sudden deterioration in kidney function that is caused by the administration of an iodine-based contrast medium; therefore, it is a subgroup of PC-AKI (see the chapter PC-AKI: Definities, terminologie en klinisch verloop in the guideline Veilig gebruik van contrastmiddelen (NVVR, 2017)). The authors defined AKI, in accordance with the KDIGO classification system, as a serum creatinine (SCr) increase of ≥26.4 micromol/L within 48 h or of ≥150 % from baseline presumed to have occurred within the prior 7 days or as oliguria (urine output of <0.5 ml/kg/h for ≥6 h). Baseline renal function was based on the baseline Cr and estimated glomerular filtration rate at the time of contrast media injection; any degree of AKI within 48 h was considered contrast-associated nephropathy. 346 paediatric patients received an iodine-based contrast media injection as part of a CT scan between January 2005 and September 2014. 233 patients had renal function assessment before and following contrast media injection and were included in the analysis. Median patient age was 5.9 years with an CI-AKI incidence of 10.3% (95%CI: 6.4 to 14.2%). There were few patients with comorbidities that could be potential risk factors, including thirteen patients with prematurity, eight with pre-existing chronic kidney disease, two with a history of glomerular disease without renal dysfunction and no patient with diabetes. The authors did report extracting information about trisomy 21 or congenital anomalies of the kidney Guideline Safe Use of Contrast Media part 4 Guideline for Authorisation phase June 2024 27 and urinary tract (CAKUT) from the charts. Vasopressor medication was used in 14 of 233 patients (6%). Nephrotoxic medication use (non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, starches or iodine-based contrast media within 72h) was more common, occurring in 83 of 233 patients (36%). To identify risk factors for CI-AKI conditional forward logistic regression analyses were performed. The model included

clinically relevant variables and variables yielding a P value of ≤0.20 in a bivariate analysis, the latter being maintained in the final model. Authors tested for co-linearity and interactions as well as assessing goodness of fit of the logistic regression with the Hosmer-Lemeshow test.

Results

*PC-AKI*

In Cantais (2016), 24 of 233 included patients (10.3 %; 95%CI 6.4 to 14.2%) developed CI-AKI. Nine of these 24 (38 %) had no previous history of chronic kidney disease, concomitant use of nephrotoxic agents or hypovolemia. Conditional forward logistic regression analysis found no factors independently associated with CI-AKI (Table 1).

Table 1. Odds ratio (OR) and 95% confidence interval (95%CI) from forward conditional logistic regression analysis of factors associated with CI- AKI (Cantais 2016).

| | **OR** | **95%CI** |
|---|---|---|
| Hypovolemia or shock at contrast-media infusion | 1.98 | 0.78 to 5.05 |
| Underlying chronic kidney disease | 3.16 | 0.53 to 18.6 |
| Cumulative number of nephrotoxic agents | | |
| None | Reference group | |
| 1 | 0.93 | 0.32 to 2.68 |
| ≥2 | 3.63 | 0.86 to 15.40 |

*Complications of PC-AKI*

No studies describing complications of PC-AKI were included in the analysis of the literature.

Level of evidence of the literature

*PC-AKI*

The level of evidence regarding the outcome measure PC-AKI started as GRADE low due to the observational nature of the included study (Cantais, 2016), and was downgraded by one level to very low due to the small number of included patients (imprecision).

*Complications of PC-AKI*

The level of evidence could not be determined as no studies describing complications of PC-AKI were included in the analysis of the literature.

## Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: Do prematurity, trisomy 21, diabetes, CAKUT, renovascular medication, or nephrotoxic medication increase the risk of developing PC-AKI in children receiving intravenous contrast media?

| | |
|---|---|
| P(atients): | Children (<18 years) receiving intravascular iodine-based contrast media. |
| I(ntervention): | Risk factors: prematurity, trisomy 21, diabetes, congenital anomalies of the kidney and urinary tract (CAKUT), renovascular medication, nephrotoxic medication. |
| C(ontrol): | Absence of these risk factors. |
| O(utcome): | Post-contrast acute kidney injury (PC-AKI), complications of PC-AKI (hospitalization, start of dialysis). |

Relevant outcome measures
The guideline development group considered PC-AKI and complications of PC-AKI as critical outcome measures for decision making.

A priori, the guideline development group did not define the outcome measures listed above but used the definitions used in the studies. The guideline development group defined PC-AKI as described in the chapter PC-AKI: Definities, terminologie en klinisch verloop in the guideline Safe Use of Contrast Media, part 1 (NVVR, 2017). If authors used other definitions such as CA-AKI (contrast associated) or CI-AKI (contrast induced). We used their terminology for the description of the study, but for the purposes of the guideline standardized to PC-AKI.

The guideline development group defined the following as a minimal clinically (patient) important difference:
• Post-contrast acute kidney injury (PC-AKI): relative risk <0.91 or >1.10. Guideline Safe Use of Contrast Media part 4 Guideline for Authorisation phase June 2024 26
• Complications of PC-AKI (hospitalization, start of dialysis): relative risk <0.91 or >1.10.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 1990 until 27-03-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 210 hits.

Studies were selected based on the following criteria:
• Systematic review, randomized controlled trial or observational research comparing risk factors to absence of risk factors for the risk of PC-AKI in children receiving intravascular iodine-based contrast.
• Children (<18 years) who underwent radiological examination using intravascular iodine-based contrast media (including radiological examination during percutaneous angiography).
• Potential risk factors related either to patient characteristics and/or treatment characteristics and/or iodine-based 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 PCAKI (hospitalization, start of dialysis, mortality).

Eight studies were initially selected based on title and abstract screening. After reading the full text, 7 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 1 study was included.

Results

One study by Cantais (2016) was included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

## Verantwoording

Laatst beoordeeld : 01-12-2024

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

## Referenties

Cantais, A. and Hammouda, Z. and Mory, O. and Patural, H. and Stephan, J. L. and Gulyaeva, L. and Darmon, M. Incidence of contrast-induced acute kidney injury in a pediatric setting: a cohort study. Pediatric Nephrology. 2016; 31 (8) :1355-1362.
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Gilligan, L. A. and Davenport, M. S. and Trout, A. T. and Su, W. and Zhang, B. and Goldstein, S. L. and Dillman, J. R. Risk of Acute Kidney Injury following Contrast-enhanced CT in Hospitalized Pediatric Patients: A propensity score analysis. Radiology. 2020; 294 (2) :548-556
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# Hydration Strategies in the Prevention of PC-AKI

## Uitgangsvraag

Welke hydratiestrategie dient te worden toegepast bij kinderen die intravasculair jodiumhoudend contrastmiddel toediening ondergaan en een hoog risico op contrast-geassocieerde acute nierschade (PC-AKI) hebben?

## Aanbeveling

Pas de volgende risico reducerende optie toe voor alle kinderen > 1 maand oud die een intravasculaire jodiumhoudend CM-toediening ondergaan:

- Staak NSAID's voorafgaand aan de jodiumhoudende contrast toediening.
- Overweeg ACEi, ARBs en diuretica te staken, na overleg met de hoofdbehandelaar.
- Bespreek met de hoofdbehandelaar de mogelijkheid om nefrotoxische medicatie, zoals aminoglycosiden, te staken voorafgaand aan het onderzoek.
- Streef naar een euvolemische status bij elk kind, ongeacht de eGFR, in het bijzonder bij kinderen met tekenen van een gecompromitteerde circulatie (sepsis/shock).

Afhankelijk van eGFR (als eGFR niet bekend is, pas advies bij eGFR >60ml/min/1.73m$^2$ toe):

- eGFR >60 ml/min/1.73m$^2$ (inclusief alle kinderen zonder eGFR):
  - Adviseer om op de dag voor en de dag van het onderzoek adequaat te drinken
- eGFR 30-60 ml/min/1.73m$^2$:
  - Dien voorafgaand aan het onderzoek 10 ml/kg/uur NaCl 0.9% IV in 1 uur toe (naast het standaard vochtbeleid of vochtinname van het kind).
  - Overleg laagdrempelig met een kinderarts-nefroloog.
- eGFR <30 ml/min/1.73m$^2$:
  - Overweeg onderzoek zonder contrast of andere onderzoeksmodaliteit.
  - Dien voorafgaand aan het onderzoek 10 ml/kg/uur NaCl 0.9% IV in 1 uur toe.

    Dien toe:
    $NaHCO_3$ 1.4%, 3 ml/kg/uur IV gedurende 1 uur vooraf aan CM-toediening, of
    *(alternatieve optie)* $NaHCO_3$ 1.4%, 3ml/kg/uur IV (max 250 mL in totaal) gedurende 1 uur vooraf aan CM-toediening en 1ml/kg/uur IV (max 500mL in totaal) gedurende 6 uur na CM-toediening.

  - Overleg met een kinderarts-nefroloog.
  - Bepaal serum kreatinine binnen 2 tot 7 dagen na contrasttoediening.

OVERWEEG bij alle neonaten (baby < 1 maand) en vroeggeboren baby's jonger dan gecorrigeerde post amenorroe duur van 44 weken bovenstaande maatregelen in overleg met de hoofdbehandelaar / kinderarts-neonatoloog.

## Overwegingen

Pros and cons of the intervention and quality of the evidence

The guideline development group conducted a systematic review of hydration strategies to reduce PC-AKI and PC-AKI related complications after iodine-based contrast media administration in children. No articles were found that met the inclusion criteria. Therefore, no conclusions could be drawn about the effects of hydration strategies on the development of PC-AKI and complications related to PC-AKI (hospitalization, dialysis). Therefore, a knowledge gap exists on this topic in children.

As there are no comparative studies investigating the research question, the recommendations in this national guideline are primarily based on the guideline for hydration and complications in the prevention of PC-AKI in adults (NVVR, 2017) and on reviews of PC-AKI in the paediatric population. Unfortunately, hard scientific evidence in children is lacking, therefore recommendations are based on expert-opinion and on reviews of paediatric PC-AKI.

In children, a low prevalence of underlying kidney disease should be balanced with possible long-term effects of AKI in children (see risk factors for PC-AKI). Based on cost and long-term patient perspective, hydration strategies should be focused on the small group of children with diagnosed or high risk of underlying kidney disease.

Most children have a normal kidney function and no underlying renal disease. The small patient group with known kidney disease or high risk for kidney disease based on past medical history should have their kidney function tested (also see module “Risk stratification in the prevention of PC-AKI”). A cut-off value eGFR < 30 ml/min/1.73m$^2$ is advised for prehydration strategies in adults (NVvR, 2017).
The risk of PC-AKI in the adult population increases with each stepwise increase of chronic kidney disease stage, with reported incidence of 5% at eGFR greater than 60 ml/min/1.73m2, up to a incidence of 30% in patients with eGFR < 30 ml/min/1.73m2. Calle-Toro (2022) published a retrospective cohort study in children undergoing CT scans with or without contrast media, showing a difference in risk between contrast exposed and non-contrast exposed groups in children with an eGFR < 60 prior to imaging. Given the possible long-term effect of nephron loss in any episode of AKI, especially in children, we recommend using a cut-off value eGFR < 60 ml/min/1.73m2 for prehydration strategies in children.

Based on the adult literature and guidelines, prehydration with IV $NaHCO_3$ 1.4% is recommended over IV Saline 0.9% because of the added benefit of higher tubular pH leading to a decreased cellular apoptosis in the setting of reactive oxygen species (ROS) formation.

Some classes of drugs can impair/reduce the perfusion pressure of the kidneys. The most commonly used classes include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics and non-steroidal inflammatory drugs (NSAIDs). Used solely, combined or in the presence of a hypovolemic state, they bring the added risk of impaired renal perfusion pressure, thereby increasing the risk of developing PC-AKI.
Their use in children is uncommon and in general limited to complicated disease. Therefore, this patient group is difficult to compare to adults, mandating a more cautious approach in its use prior to imaging with iodine-based contrast media. We recommend withholding this medication prior to imaging with iodine-based contrast media in children, after consultation with the referring physician.

Patient (and their caretakers) values and preferences
Parents and patients want to make decisions based on evidence and best clinical practice. This module provides guidance to doctors, parents, and patients to help in this decision process. The aim of this guideline is to decrease the small chance of PC-AKI in vulnerable children, although hard scientific evidence is lacking.

Costs
Only a small group of children is at increased risk of PC-AKI and the costs of hydration therapy is low. Reducing the incidence of PC-AKI in a high-risk group may help prevent future healthcare costs due to long-term consequences of PC-AKI in young children.

Acceptance, feasibility and implementation
As only a small group of children are at increased risk of PC-AKI, the acceptance, feasibility, and implementation are not expected to meet obstruction. The intervention is brief and does not require additional handling (child already has intravenous access for the procedure itself).

Rationale of the recommendations: arguments for and against the interventions
Although extensive literature exists on the prevention of PC-AKI in adults, no evidence is known in children. In the process of coming to a recommendation the key arguments to weigh were patient safety on one side versus practical feasibility on the other side. Particularly in ill children interventions should be highly effective and the risk of PC-AKI should outweigh the possible side effects of an intervention. Therefore, it was decided that all children with an eGFR<30 ml/min/1.73m$^2$ who will receive intravascular iodine-based CM, should be prehydrated with $NaHCO_3$ 1.4% at a rate of 3ml/kg/h during 1 hour before CM administration.

## Onderbouwing

## Achtergrond

When it comes to prevention of post contrast acute kidney injury (PC-AKI), the cornerstone is hydration (volume expansion). For adults, there are clear evidence-based guidelines on when to apply what kind of hydration. For children, there are none. The goal is to find out what the evidence is, specifically in children, to prevent PC-AKI, with emphasis on which eGFR cut-off value must be used in children for hydration in order to prevent PC-AKI and what the optimal hydration strategy in children is.

## Conclusies / Summary of Findings

| | |
|---|---|
| **- GRADE** | No evidence was found regarding hydration strategies to diminish PC-AKI in children (<18 years of age) undergoing radiological examinations with intravascular iodine-based contrast media. |

| | |
|---|---|
| **- GRADE** | No evidence was found regarding hydration strategies to prevent PC-AKI related complications for which hospitalization or dialysis was needed in children (<18 years of age) undergoing radiological examinations with intravascular iodine-based contrast media. |

## Samenvatting literatuur

Description of studies
No studies were included in the analysis of the literature.

Results
No studies were included in the analysis of the literature.

Level of evidence of the literature
The level of evidence could not be determined as no studies were included in the analysis of the literature.

## Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the effects of hydration versus no hydration in a child receiving intravascular iodine-based contrast media on the risk of PC-AKI and PC-AKI-related complications?

| | |
|---|---|
| P(atients): | Children (<18 years) undergoing radiological examinations with iodine-based contrast media. |
| I(ntervention): | Hydration with intravenous (IV) saline, hydration with intravenous bicarbonate, oral hydration, hydration, pre- and posthydration. |
| C(ontrol): | One of the hydration methods described above or no hydration. |
| O(utcome): | Post contrast acute kidney injury (PC-AKI), complications of PC-AKI (hospitalization, start of dialysis). |

Relevant outcome measures
The guideline development group considered PC-AKI and complications of PC-AKI as critical outcome measures for decision making.

A priori, the guideline development group did not define the outcome measures listed above but used the definitions used in the studies. The guideline development group defined PC-AKI as described in the chapter Definities, terminologie en klinisch verloop in the guideline Safe Use of Contrast Media, part 1 (NVVR, 2017). If authors used other definitions such as CA-AKI (contrast associated) or CI-AKI (contrast induced). We used their terminology for the description of the study, but for the purposes of the guideline standardized to PC-AKI.

The guideline development group defined the following as a minimal clinically (patient) important difference:

- Contrast-associated acute kidney injury (PC-AKI): relative risk <0.91 or >1.10;
- Complications of PC-AKI (hospitalization, start of dialysis): relative risk <0.91 or >1.10;

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 1990 until 04-04-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 192 hits.
Studies were selected based on the following criteria:

- Systematic review, randomized controlled trial, or observational research comparing hydration strategies for PC-AKI in children receiving intravascular iodine-based contrast media.
- Children (<18 years) who underwent radiological examinations with iodine-based contrast media.
- Hydration types: hydration with IV NaCl, hydration with IV bicarbonate, oral hydration, pre-hydration, pre- and posthydration.
- Follow-up time after hydration was at least 48 hours.
- At least one of the outcome measures was described: PC-AKI, complications of PC-AKI (hospitalization, start of dialysis, mortality).

Four studies were initially selected based on title and abstract screening. After reading the full text, all studies were excluded (see the table with reasons for exclusion under the tab Methods).

Results
No studies were included in the analysis of the literature.

## Verantwoording

Laatst beoordeeld : 01-12-2024

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

## Referenties

NVvR, 2017. Richtlijn Veilig gebruik van contrastmiddelen - Module Hydratie en complicaties. Beoordeeld: 01-11-2017.
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Maloney E, Iyer RS, Phillips GS, Menon S, Lee JJ, Callahan MJ. Practical administration of intravenous contrast media in children: screening, prophylaxis, administration, and treatment of adverse reactions. Pediatr Radiol 2019; 49(4): 433-447.

# Prophylaxis of hypersensitivity reactions

## Uitgangsvraag

Welke profylactische maatregelen moeten worden genomen bij kinderen (<18 jaar) met een verhoogd risico op overgevoeligheidsreacties na toediening van jodiumhoudende contrastmiddelen?

## Aanbeveling

Overweeg een alternatieve beeldvormingsmodaliteit bij alle patiënten met een (gedocumenteerde) geschiedenis van een overgevoeligheidsreactie voor een contrastmiddel. Indien dit niet mogelijk is, overweeg het uitvoeren van het onderzoek zonder contrastmiddel, indien de reductie van diagnostische kwaliteit acceptabel is.

- Indien de vorige overgevoeligheidsreactie mild* was:

Voer het radiologisch onderzoek uit zoals gebruikelijk gezien het lage risico op het ontwikkelen van een meer ernstige reactie.
Bij twijfel aan de ernst van de vorige overgevoeligheidsreactie: overweeg om de patiënt te verwijzen naar een allergoloog.

- Indien de vorige overgevoeligheidsreactie matig tot ernstig** was:

Verwijs patiënt naar een allergoloog. Indien mogelijk, stel het beeldvormend onderzoek uit totdat de resultaten van de huidtesten bekend zijn. Pas het advies van de allergoloog toe met betrekking tot het kiezen van een alternatief contrastmiddel.

- Indien acuut onderzoek noodzakelijk is:

Kies voor een alternatief contrastmiddel (obv lage kruisreactiviteit) of een alternatieve beeldvormingsmodaliteit zoals eerder beschreven. Indien het verdachte contrastmiddel van een eerdere reactie niet bekend is of er geen alternatief gegeven kan worden, wordt geadviseerd eerst 10% van de contrastmiddeldosis te geven. Observeer de patiënt minimaal 30 min met een infuus alvorens de overige 90% toe te dienen. Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie (zie module behandeling acute overgevoeligheidsreactie). De kans op een allergische reactie is heel klein en de kans op een eventuele ernstige allergische reactie wordt zo nog verder verkleint.

*milde reacties: alleen symptomen van de huid (erytheem, enkele urticaria, mild angio-oedeem, jeuk), rhinitis en/of conjunctivitis, niezen, kriebel in de keel.

**matig tot ernstige reacties: gegeneraliseerde urticaria, respiratoire klachten met stridor (expiratoir en/of inspiratoir), heesheid, zwelling van de tong en/of pharynx, herhaaldelijk braken, hypotensie, bewustzijnsverlies, shock.

NB bovenstaande laat het belang van een goede documentatie van symptomen van de reactie zien. Documenteer de naam en dosis van het gebruikte contrastmiddel in het radiologische verslag van het onderzoek en/of bij de beelden van het onderzoek.

## Overwegingen

Pros and cons of the intervention and quality of evidence
The guideline development group conducted a systematic review of the optimal prophylactic treatment for acute and delayed hypersensitivity reactions to contrast agents. No articles were found that met the inclusion criteria. In most studies that included children and adults the average age was over 50 years and only few children were included. Therefore, no conclusions could be drawn about the effects of prophylactic treatments to prevent allergic / hypersensitivity reactions to contrast material in children. Consequently, a knowledge gap exists on this topic. A recent review however, suggests to be cautious about the use of corticosteroid premedication (Maloney, 2019).

As there are no comparative studies investigating the research question, the recommendations in this national guideline are based mainly on the guideline for prophylactic measures to prevent hypersensitivity reactions to contrast in adults (NVVR, 2022).

Literature shows that the prevalence of hypersensitivity reaction in children is very low, they experience less hypersensitivity reactions to contrast media compared to adults (Endrikat, 2022). In addition, severe reactions are very rare in children. A large retrospective study in the US found an incidence of 0.46% hypersensitivity reactions to contrast material in 12,494 patients. Most of these were mild (47 of 57 in total) and no severe reaction (Callahan, 2009). However, severe reactions with anaphylaxis have been described in pediatric patients (Dillman, 2007). In case of a severe reaction intramuscular adrenalin administration is the main treatment (see the module about Treatment of acute hypersensitivity reaction in children).

*Pharmacologial prevention*
For adults the evidence in the guideline regarding the effectivity for pharmacological prevention is very heterogeneous and of low quality. Prophylactic premedication mainly reduces the number of mild reactions and therefore the total number of reactions, but not the number of severe reactions. There is no evidence that this is different in children. One recent meta-analysis with five studies in patients with previous moderate to severe hypersensitivity reactions described a reduction in reactions with steroid premedication. However, there were several study limitations and only a few children were included (Hsieh, 2022). Therefore, in line with the Dutch guideline for adults, the guideline development group does not recommend premedication for children.

In line with the Dutch guideline for adults, major international guidelines do not recommend the use of premedication for non-severe nonimmediate reactions, however in case of more severe reactions they suggest performing allergologic skin testing and referral to an allergist (ACR, 2023; ESUR, 2018; Shaker 2020; Torres, 2021).

*Antihistamines and corticosteroids*

If premedication is required, two types of drugs are used: H1-antihistamines and corticosteroids. Often, they are used concomitantly, making their individual effect difficult to assess, particularly since there are many variations in premedication schedules. However, both have side effects that one should be aware of.

H1-antihistamines block histamine receptors on various effector cells, blocking the effect of one of the pivotal players in direct mast cell responses. However, mast cells and basophils secrete various other substances that are not blocked by these drugs. The main side effect of the older H1-antihistamines that are available for intravenous administration is drowsiness/sedation, but they also have a negative effect on blood pressure. Clemastine (Tavegyl) is one of the H1-antihistamines that is still widely used in treating allergic symptoms or as premedication and should be used with caution for this reason. For the newer nonsedating antihistamines this effect is usually mild, but these are mainly available for oral administration.

Corticosteroids have various effects on the immune system, including mast cells, and therefore can block both mast cell degranulation by upregulating inhibitory signaling receptors, and inhibit cytokine production through suppression of gene transcription. (Andrade, 2004; Park, 2009) These membrane stabilizing effects require that administration is started >6h before contrast media administration. Unfortunately, this comes with a less favourable side effect profile, particularly with higher doses and repeated exposure. It has been shown that corticosteroid premedication can cause brief hyperglycaemia (Davenport, 2010), but may also be associated with longer hospital stay, increased costs, and worse clinical outcomes (Davenport, 2016).

There are two widely used premedication protocols; the Greenberger and Lasser protocol in which high doses of corticosteroids and antihistamines (diphenhydramine) are used. (Greenberger, 1981; Greenberger, 1986; Lasser, 1994). In the Netherlands steroids and clemastine (Tavegyl®) are frequently used as premedication in elective procedures. There is no literature available to establish an optimal indication or protocol.

*Pediatric medication dose:*

- Prednisolone 1mg/kg with a max of 20 mg IV. 12h and 2h before the procedure.
- Clemastin IV 25-50 microgram/kg/dose with a max of 2mg. 1h before the procedure (Tmax within minutes). Note: this can give drowsiness/sedation.

In conclusion, there is a paucity of data on the benefits of premedication for hypersensitivity reactions in adults and even less in paediatric patients. Most of these reactions are self-limiting or can be treated symptomatically. In patients with a (documented) history of a hypersensitivity reaction to a contrast medium, an alternative imaging modality should be considered. The more severe the reaction, the stronger omitting a contrast medium should be considered. For mild reactions in which alternative imaging modalities are of substantially inferior quality, the risk – benefit ratio may shift. In many cases, CT with iodine-based contrast media can be replaced by ultrasound, with or without contrast agents, or MRI, with or without contrast agents. When this is not possible, consider performing the examination or imaging study without a contrast medium or with an alternative contrast medium (see next paragraph), but only if this has an acceptable degree of diagnostic quality. For this, close communication with the referring specialist is mandatory. Finally, in case of a suspected hypersensitivity, patients should be referred to a paediatric allergist.

*Cross-reactivity between iodine-based contrast media (ICM):*
Schrijvers (2018) found most cross-reactivity between agents with a N-(2,3 dihydroxypropyl)-carbamoyl side chain. This side chain is present in most media used in The Netherlands (Iopromide, Iohexol, Iomeprol, Ioversol and Iodixanol), but not in Iobitridol and Iopamidol. The table below shows **cross-reactivity rates between pairs of ICM in skin positive patients with immediate hypersensitivity reactions.** Risk of cross-reactivity is marked as very low (dark green, <10%), low (green, 10-20%), medium (orange 20-30%), high (red, 30-50%) and very high (dark red, >50%).

| ICM name | *Iobtridol* | *Iopramidol* | *Iopromide* | *Iohexol* | *Iomeprol* | *Ioversal* | *Iodixanol* |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| *Iobtridol* | X | | | | | | |
| | | | | | | | |
| *Iopramidol* | **11.8%** [5.5-18] | X | | | | | |
| | | | | | | | |
| *Iopromide* | **22.1%** [22-22.2] | **25.6%** [11.1-40] | X | | | | |
| | | | | | | | |
| *Iohexol* | **20.8%** [16.6-25] | **25.1%** [11.1-39] | **43.5%** [38.9-48] | X | | | |
| | | | | | | | |
| *Iomeprol* | **17.6%** [13-22.2] | **33.2%** [33-33.3] | **38.7%** [33-44.4] | **40.2%** [36-44.4] | X | | |
| | | | | | | | |
| *Ioversal* | **20.6%** [19-22.2] | **35.6%** [22.2-49] | **37.7%** [33.3-42] | **50.0%** [38.9-61] | **53.3%** [51-55.5] | X | |
| | | | | | | | |
| *Iodixanol* | **19.3%** [16.6-22] | **36.6%** [22.2-51] | **45.5%** [38.9-52] | **51.7%** [44.4-59] | **45.5%** [41-50] | **51.5%** [38.9-64] | X |

Table 1: **Cross-reactivity rates between pairs of ICM in skin positive patients.**The guideline for prophylactic measures to prevent hypersensitivity reactions to contrast in adults (NVVR, 2022).

*Documentation of contrast medium*
To prevent administration of a specific contrast media that previously triggered an allergic reaction, proper documentation in the electronic patient record (EPR) has become very important. In line with the recommendation in the guideline for prophylactic measures to prevent hypersensitivity reactions to contrast in adults (NVVR, 2022), the guideline development group recommends documenting the specific contrast medium name and dose which were administered to the patient in the imaging report and/or with the stored images.

Patient (and their caretakers) values and preferences
Allergic reactions can be a cause of concern for patients and their caregivers, especially if they have experienced allergic reactions in the past. It is important to inform patients that allergic reactions to contrast media are extremely rare in pediatric patients. Patients with previous allergic reactions often expect precautionary steps, but this is not always indicated. Time should be taken to discuss the reasoning for adapting the procedure (or not). There is no evidence that premedication reduces the risk of severe reactions. In case of a severe reaction, it is best to use a substitute contrast medium and when there is enough time to consult an allergist. It's important to document previous reactions with timing of onset and type of symptoms, preferably with pictures of skin reactions. This helps the allergist to classify the type of hypersensitivity reaction and subsequently to give a good advice.
In case of an underlying disease like eczema of chronic spontaneous urticaria it is advised to inform the patient that the procedure can cause an increase in symptoms and patients should use their own medication more intensively before and after the procedure.
In case of using premedication, patients should be warned regarding the side effects of corticosteroids and clemastine. Second generation antihistamines have less side effects.

Costs
Severe hypersensitivity reactions are associated with additional healthcare costs. Currently physicians are likely to be extra careful in children and thus order additional (and often unnecessary) premedication and interventions for all children who have a hypersensitivity reaction in their history. The recommendations in this guideline can prevent unnecessary use of premedication in specific subgroups (such as for non-severe nonimmediate reactions), while simultaneously preventing unnecessary incidents of hypersensitivity reactions. In addition, there is evidence that corticosteroid premedication can enhance a prolonged hospital stay (Davenport 2017)

Acceptability, feasibility and implementation
The guideline development group does not anticipate any acceptance issues. The recommendations in the current guideline address longstanding uncertainty about the need for prophylactic measures to prevent hypersensitivity reactions. Therefore, it will contribute to a more unified and equal approach in children.

Rationale of the recommendations: weighing arguments for and against the interventions
There is a paucity of data on the benefits of prophylactic measures including premedication for prevention of recurrent hypersensitivity reactions in paediatric patients. Hypersensitivity reactions are very rare and most of these reactions are classified as mild and self-limiting.

In patients with a (documented) history of a hypersensitivity reaction to a contrast medium, an alternative imaging modality or a different contrast medium should be considered. In case of a more severe reaction a paediatric allergist should be consulted additionally. This recommendation contributes to a more unified and equal approach for prophylactic measures to prevent hypersensitivity reactions in children. One should be aware of unnecessary use of premedication in specific subgroups. Physicians are likely to accept the current recommendations, but it will be important to carefully inform patients and their caregivers regarding the low risk and possible side effects of premedication. Especially those patients who have experienced a mild allergic reaction in the past.
The risk of a severe allergic reaction is very rare, however staff should be trained how to treat and handle possible allergic symptoms that can occur.

## Onderbouwing

## Achtergrond

The incidence of hypersensitivity reactions to Iodinated contrast administration is 0.18-0.46% in paediatric patients (Callahan, 2009; Dillman 2007). The incidence decreased after the switch to non-ionic iodine-based contrast media, which are the only ones still used in the Netherlands. Most of these reactions are mild to moderate, while severe reactions are very rare, especially in children. The most important risk factor for an allergic-like reaction is an history of an allergic reaction to contrast media. There is no consensus with respect to the prophylactic treatment in children with a higher risk of hypersensitivity reactions to contrast media. Furthermore, the current guideline “Safe use of contrast media” lacks advice regarding the treatment in pediatric patients in clinical practice.

## Conclusies / Summary of Findings

| | |
|---|---|
| **- GRADE** | No evidence was found regarding the effect of prophylactic measures to prevent allergic / hypersensitivity reactions to contrast in children (<18 years of age) undergoing radiological examinations. |

## Samenvatting literatuur

Description of studies
No studies were included in the analysis of the literature.

Results
No studies were included in the analysis of the literature.

Level of evidence of the literature
The level of evidence could not be determined as no studies were included in the analysis of the literature.

## Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
Which prophylactic treatments should be used in children (<18 years) undergoing radiological examinations with iodine-based contrast agents to prevent symptoms of hypersensitivity reactions compared to other or no treatments?

| | |
|---|---|
| P(atients): | Children (<18 years) undergoing radiological examinations with iodine-based contrast media. |
| I(ntervention): | Prophylactic measure to prevent hypersensitivity reactions after contrast media administration. |
| C(ontrol): | No prophylactic measure or a different prophylactic measure to prevent hypersensitivity reactions after contrast media administration. |
| O(utcome): | Allergic reactions to contrast media, hypersensitivity reactions, type I/ type IV, severe allergic reaction. |

Relevant outcome measures
The guideline development group considered allergic / hypersensitivity reactions to contrast as critical outcome measure for decision making.

A priori, the guideline development group did not define the outcome measures listed above but used the definitions used in the studies.

The guideline development group defined the following as a minimal clinically (patient) important difference:

- allergic / hypersensitivity reactions to contrast: relative risk ≤0.8 or ≥1.25 (dichotomous); 0.5 SD (continuous)

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 1990 until 24-02-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 201 hits. Studies were selected based on the following criteria:

- Systematic review, randomized controlled trial, or observational research comparing prophylactic measures to prevent hypersensitivity reactions after contrast administration to other or no prophylactic measurements.
- Including children (<18 years) undergoing radiological examinations with contrast media.
- Reports predefined outcome measure: allergic / hypersensitivity reactions to contrast.

53 studies were initially selected based on title and abstract screening. After reading the full text, all studies were excluded (see the table with reasons for exclusion under the tab Methods), and no studies were included.

Results
No studies were included in the analysis of the literature.

## Verantwoording

Laatst beoordeeld : 01-12-2024

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

## Referenties

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# Treatment of acute hypersensitivity reaction

## Uitgangsvraag

Wat is de optimale behandeling voor acute overgevoeligheidsreacties op contrastmiddelen?

## Aanbeveling

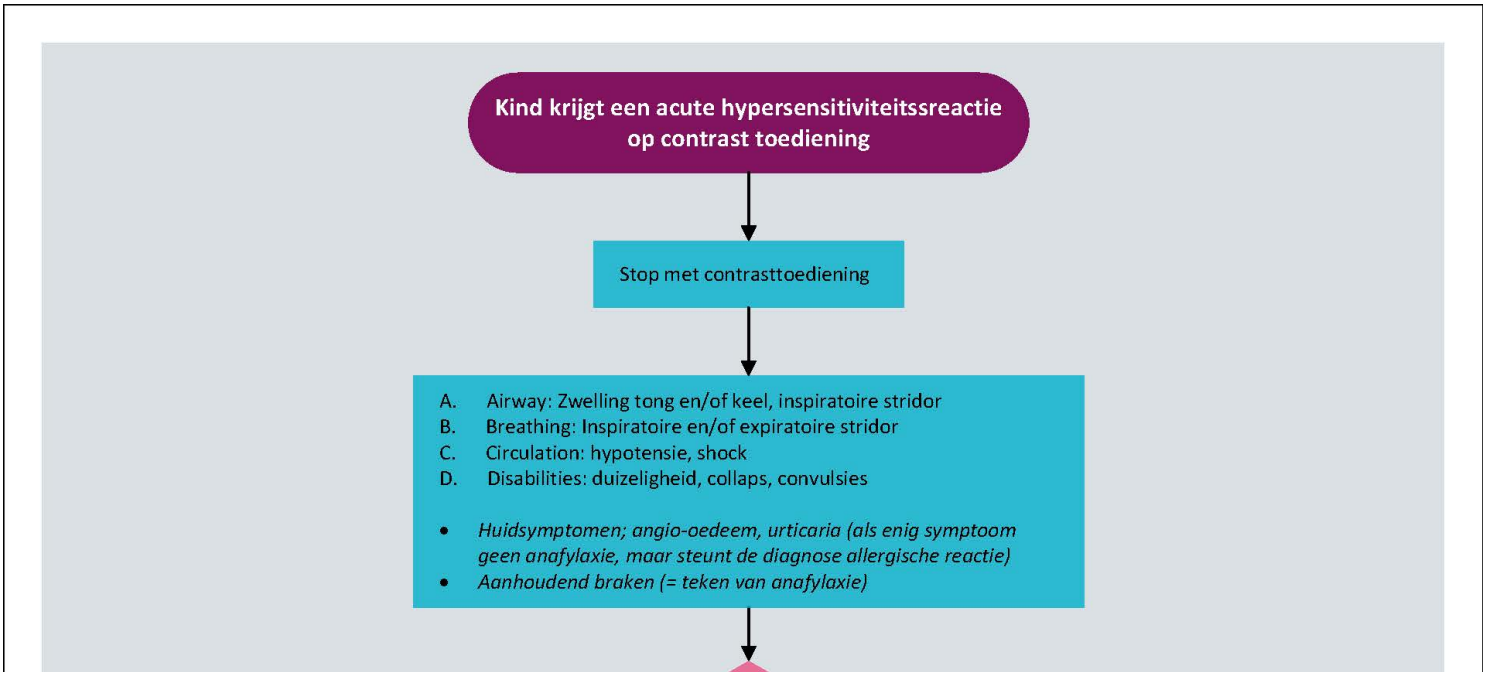
Acute allergische reacties verschillen in ernst; de aanbevelingen zijn per ernst van de situatie geformuleerd.

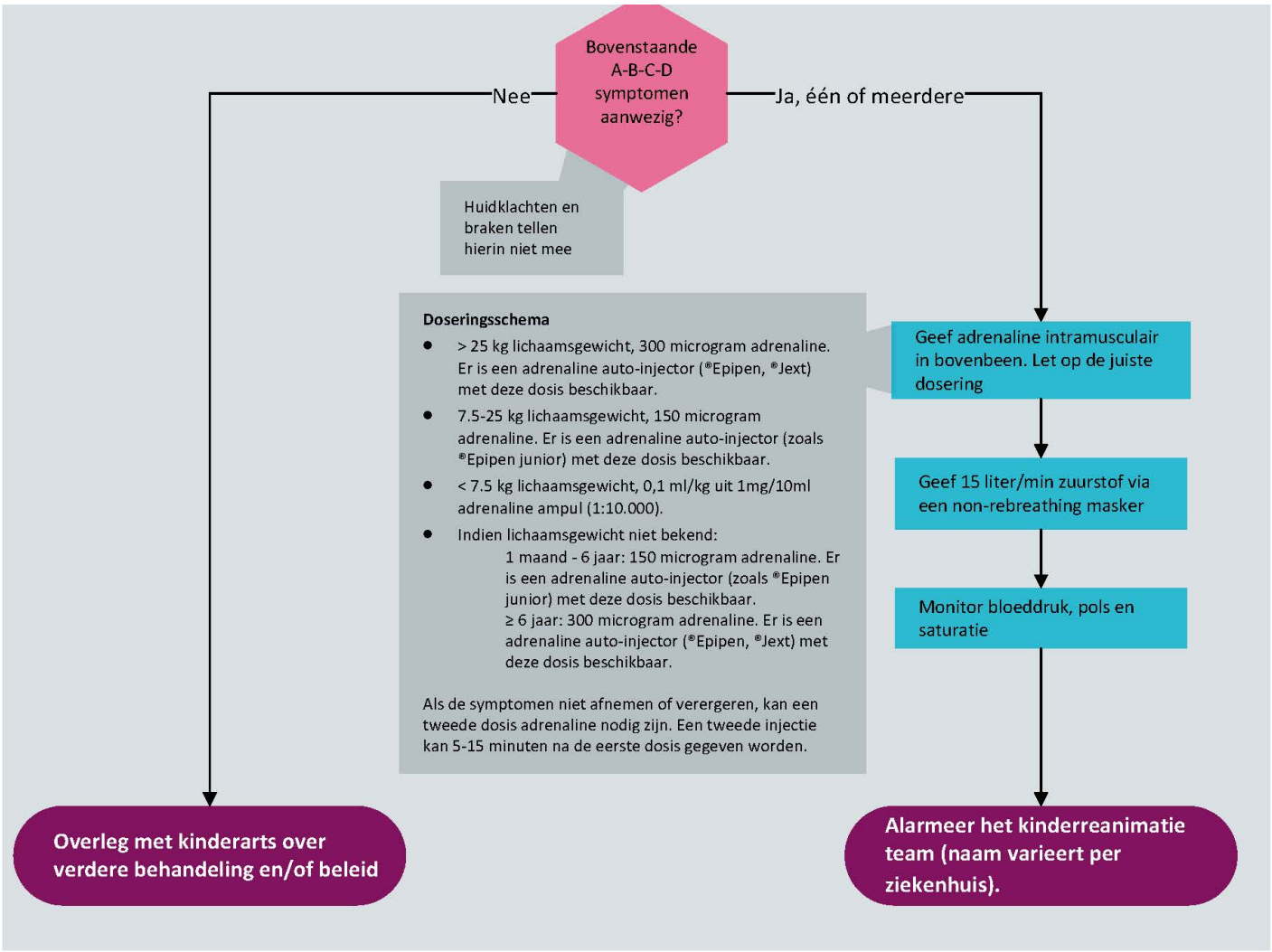
*Bij anafylactische reactie:*

- Geef adrenaline intramusculair. Let op de juiste dosering:
  - >25 kg lichaamsgewicht 300 microgram adrenaline (adrenaline auto-injectors beschikbaar, zoals de Epipen® or Jext®),
  - 7.5-25 kg lichaamsgewicht 150 microgram adrenaline (adrenaline auto-injectors beschikbaar, zoals de Epipen Junior® or Jext®),
  - < 7.5 kg lichaamsgewicht , 10 mcg/kg, overeenkomend met 0.1 ml/kg uit 1mg/10ml adrenaline ampul (1:10.000).
  - Indien het gewicht niet bekend is: ≥ 6 jaar 300 microgram (Epipen® or Jext®), < 6 jaar 150 microgram (Epipen Junior® or Jext®).
- Geef 15 liter/minuut zuurstof via een non-rebreathing masker.
- Alarmeer het (kinder)reanimatie team (naam varieert per ziekenhuis).
- Als de symptomen niet afnemen of verergeren, kan een tweede dosis adrenaline nodig zijn. Een tweede injectie kan 5-15 minuten na de eerste dosis gegeven worden.

*Bij niet-anafylactische acute overgevoeligheidsreacties:*

- Overleg met een kinderarts over verdere behandeling en/of beleid.






## Overwegingen

Advantages and disadvantages of the intervention and quality of evidence

The work group conducted a systematic review of the optimal treatment for acute hypersensitivity reactions to contrast agents. No articles were found that met the inclusion criteria. Therefore, no conclusions could be drawn about the effects of treatment for acute hypersensitivity reactions on the outcome measures duration of acute allergic reaction, severity of symptoms, morbidity, mortality, costs, ICU admission, length of stay. Therefore, a knowledge gap exists on this topic.

As there are no comparative studies investigating the optimal treatment for acute hypersensitivity reactions to contrast agents in children, the recommendations in this national guideline are based mainly on expert

opinion in combination with two other sources of relevant literature. The first is the Dutch National Advanced Paediatric Life Support book (Turner, 2022). This is considered the standard with regard to dealing with life threatening pediatric conditions, including anaphylaxis.
We also used the adult guideline for the treatment of acute hypersensitivity reactions to contrast media (NVvR, 2020). We adhere to the adult guidelines as much as possible, taking into account differences between adults and children in physiology and treatment options. First, we describe key differences to consider, followed by the treatment options.

*Differences between adults and children*

- The airways in children differ from those in adults in diameter and shape, making children especially vulnerable to airway narrowing due to anaphylaxis.
- Unlike adults, children in general have better developed mechanisms of compensation. Unfortunately, the degree of sickness can easily be underestimated.
- In children medication is based on body weight in kilograms. If this is unknown, age is used as a surrogate to estimate body weight.
- Like in adults, APLS guidelines with an ABC-type approach is used (NVvR, 2020).

*Acute hypersensitivity reactions*
Patients who develop an acute hypersensitivity reaction to contrast agents may have a variety of symptoms. Varying from mild symptoms, for example a rash, to severe potentially life-threatening reactions with symptoms like (airway) edema, inspiratory and expiratory stridor, hypotension, collapse and persistent vomiting. These severe reactions are also called anaphylaxis. Since the frequency of severe hypersensitivity reactions to contrast agents is quite rare, the guideline development group focuses on three simple but effective ways to stabilize the patient while waiting for a pediatric resuscitation team. Further treatment is best done by a pediatrician or pediatric anesthesiologist. The three measures to treat anaphylaxis are described in more detail below. For non-anaphylactic acute hypersensitivity reactions to contrast agents, the guideline development group recommends consulting a pediatrician.

*Three measures to treat anaphylaxis*
Anaphylaxis or severe hypersensitivity reactions are potentially life-threatening and it is important to start treatment as soon as possible. Quick administration of intramuscular adrenaline will swiftly alleviate symptoms. The second most important treatment will be administration of 15 liter per minute of oxygen, via a non-rebreathing mask. It is important to have smaller masks suitable for children on hand in the CT room. However, since the effect of the adrenaline may be temporary, specialized pediatric care is required. So third, a (pediatric) resuscitation team needs to be called to assist immediately (the exact name and composition of this team differs between hospitals). The goal of treatment for anaphylaxis is to stabilize the patient, while waiting for a pediatric resuscitation team. Further recommendations regarding the treatment of children with hypersensitivity reactions are beyond the scope of this guideline. Pediatricians will follow APLS guidelines for further treatment of hypersensitivity reactions.
Unlike the treatment of anaphylaxis in adults, clemastine is no longer recommended for treatment of anaphylaxis in children. It’s known to cause hypotension and drowsiness; this last side effect can further compromise airway patency.

*Adrenaline administration*
In the setting of anaphylaxis, adrenaline should be administered into the muscle (intramuscular injection). The recommended dose is:

- >25 kg body weight: 300 microgram adrenaline (adrenalin auto-injectors available, such as Epipen® or Jext®),
- 7.5-25 kg body weight: 150 microgram adrenaline (adrenalin auto-injectors available, such as Epipen Junior® or Jext®),
- < 7.5 kg body weight: 10 mcg/kg, (equals 0.1 ml/kg from 1mg/10ml adrenaline vial ( 1:10,000).
- When weight is unknown: ≥ 6 years 300 microgram (adrenalin auto-injectors available, such as Epipen® or Jext®), < 6 years 150 microgram (adrenalin auto-injectors available, such as Epipen Junior® or Jext®).
- When symptoms do not decrease or progress a second dose of adrenalin can be necessary. A second injection can be given 5-15 minutes after the first dose.

Adrenaline is available in vials, from which the solution must be aspirated into a syringe before it can be administered to the child. Another option is to use an adrenalin auto-injector, in which an adrenaline solution is already in a syringe. These devices can be spring loaded, such as the Epipen®. An adrenaline auto-injector is used to administer adrenaline intramuscularly in an acute setting. Since most healthcare providers in radiology do not use needles and syringes to administer medication on a daily basis, and since time is of the utmost essence, the guideline development group strongly advises use of an adrenalin auto-injector despite a higher cost (see cost paragraph below for more details).

Patient (and their caretakers) values and preferences
Acute hypersensitivity reactions to contrast media are a cause of concern for patients and their caregivers, especially if they have experienced acute hypersensitivity reactions in the past. It is important to distinguish severe reactions such as anaphylaxis from mild reactions such as rash, since treatment and response should be in proportion. In case of severe reactions, namely anaphylaxis, the focus is on swift intervention to reduce the immediate concern (airway restriction), meanwhile ensuring the correct expertise is sent by contacting a pediatric resuscitation team for any further decisions on treatment. In case of mild acute hypersensitivity reactions, there is more time to formulate a treatment strategy and, if necessary, consult the appropriate experts.

Costs
It is important to act quickly and effectively to prevent serious complications from acute hypersensitivity reactions, and reduce associated additional healthcare costs both in the short and long term. Most of the recommendations in this guideline lead no or little additional costs. Oxygen is usually already available in CT suites and non-rebreathing masks cost around 5 euros each. Only for adrenaline administration in children weighing >10 kg does the guideline development group strongly advice a higher priced alternative, based on the ease of use and thus more time efficient administration. For example, the use of adrenalin auto-injectors such as the Epipen® (cost 38-42 euros) instead of adrenaline injection using vials (3 euros for 1mg/1ml solution) (Zorginstituut Nederland, n.d.). For children weighing less than 10 kilograms, the only option is to administer the (=weight adjusted) amount of adrenaline with a syringe.

Acceptability, feasibility and implementation

The guideline development group does not anticipate any acceptance or feasibility issues. The triad adrenaline / high flow oxygen / calling for help is a simple but effective strategy in cases of anaphylactic acute hypersensitivity reactions. High oxygen flow is already standard in the treatment of anaphylactic acute hypersensitivity reactions in adults. Ensuring smaller non-rebreathing masks suitable for children are present should not provide problems as these are already used and readily available in hospital. Similarly, the guideline development group anticipates it will be feasible to ensure the way to contact the paediatric resuscitation team is clearly signposted near the CT scanner and contact details for a paediatrician are available. Regarding adrenaline, many radiology departments are already familiar with the use of an adrenalin auto-injectors. Therefore, the introduction of an Adrenaline auto-injector (for children who weigh more than 7.5 kilograms) is expected to be acceptable and feasible. If contrast media is also given to children who weigh less than 7.5 kilograms, a 0,1mg/10 ml vial of adrenaline (with needles and syringes) also needs to be present. In terms of implementation, given the rarity of these types of reactions it is important to provide adequate training of personnel on how to handle acute contrast reactions in children. Thus, ensuring the correct level of expertise is maintained to act when necessary.

Rationale of the recommendation: weighing arguments for and against the interventions

Unfortunately, there were no comparative studies investigating the optimal treatment for acute hypersensitivity reactions to contrast agents in children. Therefore, the recommendations in this national guideline are based mainly on expert opinion in combination with a current standard book on Advanced Paediatric Life Support (Turner, 2022) and the existing adult guideline for the treatment of acute hypersensitivity reactions to contrast media (NVvR, 2020).

Since the airways in children differ from those in adults in diameter and shape, this makes children especially vulnerable to airway narrowing due to anaphylaxis. To treat airway narrowing due to an anaphylactic acute hypersensitivity reaction to contrast media, adrenaline should be administered intramuscularly. In addition to this, high flow oxygen should be given by means of a non-rebreathing mask. Since anaphylaxis is a paediatric emergency, advanced paediatric life support expertise is required immediately, to further treat the child and prevent rapid deterioration of the condition of the child.

Overall, there is consensus in our guideline development group that these three basic measures (adrenaline, oxygen, call for help) are critical in the primary treatment of life-threatening anaphylaxis. In case of mild acute hypersensitivity reactions, there is more time to formulate a treatment strategy and, if necessary, consult the appropriate experts.

The guideline development group does not anticipate any acceptance, feasibility or implementation issues.

## Onderbouwing

## Achtergrond

Anaphylaxis due to intravenous contrast media is rare in children. Currently, radiologists use a combination of adult guidelines and experience to treat acute hypersensitivity reactions to contrast media in children. However, children are a heterogeneous population in terms of age and background. Children have a different

anatomy of the upper airways, making them especially vulnerable to airway constriction due to anaphylaxis. Also, since children come in different shapes and sizes, tailormade approach based on body weight and anatomical differences in comparison to adults, is required. Therefore, the current guideline describes the optimal treatment for acute hypersensitivity reactions to contrast media in children.

## Conclusies / Summary of Findings

| | |
|---|---|
| **- GRADE** | No evidence was found regarding the effect of different kinds of treatment to reduce duration of acute allergic reaction in children (<18 years of age) undergoing radiological examinations with contrast agents. |

| | |
|---|---|
| **- GRADE** | No evidence was found regarding the effect of different kinds of treatment to reduce severity of complaints of acute allergic reaction in children (<18 years of age) undergoing radiological examinations with contrast agents. |

| | |
|---|---|
| **- GRADE** | No evidence was found regarding the effect of different kinds of treatment to reduce morbidity due to acute allergic reaction in children (<18 years of age) undergoing radiological examinations with contrast agents. |

| | |
|---|---|
| **- GRADE** | No evidence was found regarding the effect of different kinds of treatment to reduce mortality due to acute allergic reaction in children (<18 years of age) undergoing radiological examinations with contrast agents. |

| | |
|---|---|
| **- GRADE** | No evidence was found regarding the effect of different kinds of treatment to reduce costs due to acute allergic reaction in children (<18 years of age) undergoing radiological examinations with contrast agents. |

| | |
|---|---|
| **- GRADE** | No evidence was found regarding the effect of different kinds of treatment to reduce hospitalization in an IC-unit due to acute allergic reaction in children (<18 years of age) undergoing radiological examinations with contrast agents. |

| | |
|---|---|
| **- GRADE** | No evidence was found regarding the effect of different kinds of treatment to reduce length of stay in hospital due to acute allergic reaction, in children (<18 years of age) undergoing radiological examinations with contrast agents. |

## Samenvatting literatuur

Description of studies

No studies were included in the analysis of the literature.

Results

No studies were included in the analysis of the literature.

Level of evidence of the literature
The level of evidence could not be determined as no studies were included in the analysis of the literature.

## Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the effects of different measures to reduce symptoms of hypersensitivity reactions in children (<18 years of age) undergoing radiological examinations with contrast media?

| | |
|---|---|
| P(atients): | Children (<18 years) with acute hypersensitivity reaction after administration of contrast media; |
| I(ntervention): | Treatment, antihistamines, corticosteroids, epinephrine, adrenalin, dopamine, norepinephrine, noradrenalin, histamine H1 antagonists, histamine H2 antagonists, H1 antihistamines, H2 antihistamines, adrenergic beta-2 receptor agonists, glucocorticoids, management/treatment of hypersensitivity reactions/allergic reactions after contrast media, antihistamines, volume resuscitation, bronchodilators; |
| C(ontrol): | Conservative treatment or comparison of interventions mentioned above; |
| O(utcome): | Curation of acute allergic reactions, severity of complaints, morbidity, mortality, costs, hospitalization in an IC-unit, length of stay. |

Relevant outcome measures
The guideline development group considered morbidity, mortality, and hospitalization in an IC-unit as critical outcome measures for decision making; and duration of acute reaction, length of stay and costs, as outcome measures for decision making.

A priori, the guideline development group did not define the outcome measures listed above but used the definitions used in the studies.

The guideline development group defined the following as a minimal clinically (patient) important difference:

- Duration of acute allergic reaction: 0.5 SD (continuous);
- Severity of complaints: 0.5 SD (continuous);
- Morbidity: relative risk <0.91 or >1.10;
- Mortality: relative risk <0.95 or >1.05;
- Hospitalization in an IC-unit: relative risk <0.80 or >1.25;
- Length of stay in hospital: 0.5 SD (continuous);
- Costs: 0.5 SD (continuous);

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 1990 until 14-03-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 147 hits. Studies were selected based on the following criteria:

- Systematic review, randomized controlled trial or observational research comparing treatment for acute

hypersensitivity reactions to conservative treatment or another kind of treatment.
- Including children (<18 years) with an acute hypersensitivity reaction after administration of contrast media.
- Reporting at least one of the following outcome measures: duration of acute allergic reaction, severity of complaints, morbidity, mortality, costs, hospitalization in an IC-unit, length of stay.

26 studies were initially selected based on title and abstract screening. After reading the full text, all studies were excluded (see the table with reasons for exclusion under the tab Methods), and no studies were included.

Results
No studies were included in the analysis of the literature.

## Verantwoording

Laatst beoordeeld : 01-12-2024

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

## Referenties

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# Monitoring of Thyroid Function after Administration of Iodine-based Contrast Media

## Uitgangsvraag

Moet bij kinderen na toediening van een jodiumhoudend contrastmiddel de schildklierfunctie gemonitord worden?

## Aanbeveling

Controleer schildklierfunctie (TSH-meting) 2 weken na toediening van *intravasculair of gastro-intestinaal* jodiumhoudend contrast, bij alle prematuur geboren kinderen (zwangerschapsduur < 37 weken) onder de leeftijd van 3 maanden.

Controleer schildklierfunctie (TSH-meting) 2 weken na toediening van *intravasculair* jodiumhoudend contrast, bij a term geboren kinderen (zwangerschapsduur ≥ 37 weken) onder de leeftijd van 3 maanden in geval van risicofactoren zoals dysmaturiteit (geboortegewicht voor zwangerschapsduur < -2 SDS), ernstige ziekte, nierinsufficiëntie, cardiale aandoening en in geval van langdurige/veelvuldige blootstelling aan jodiumhoudend contrast zoals bij coronaire CT angiografie en nierdialyse.

Overweeg controle van schildklierfunctie (TSH-meting) 2 weken na toediening van *intravasculair* jodiumhoudend contrast bij kinderen tussen de leeftijd van 3 maanden en 3 jaar in geval van risicofactoren zoals ernstige ziekte, nierinsufficiëntie, cardiale aandoening en in geval van langdurige/veelvuldige blootstelling aan jodiumhoudend contrast zoals bij coronaire CT angiografie en nierdialyse.

Interpretatie TSH-concentratie:

- TSH ≤ 5 mE/l: geen actie, tenzij het een zeer prematuur kind betreft met een berekende leeftijd van < 32 weken amenorroe duur ten tijde van de bloedafname. Herhaal in dat geval de TSH-meting na 1 week.
- TSH > 5 en ≤ 10 mE/l: herhaal TSH met vrijT4 meting na 1 week
- TSH > 10 en ≤ 20 mE/l: meet vrijT4. Een lage vrij T4 concentratie wijst op hypothyreoïdie en is een behandelindicatie. Overleg met kinderarts-endocrinoloog.*
- TSH > 20 mE/l: meet vrijT4 en start behandeling in overleg met kinderarts-endocrinoloog.*

*Interpretatie van vrij T4 wordt bemoeilijkt door transiënte hypothyroxinemie van prematuren, “non-thyroidal illness” en gebrek aan leeftijdsspecifieke referentie intervallen. Overleg met kinderarts-endocrinoloog wordt geadviseerd voordat met behandeling wordt gestart.

## Overwegingen

Advantages and disadvantages of the intervention and quality of evidence
Thyroid hormone is essential for normal brain development in children, especially in the first three years of life. It is well known that untreated congenital hypothyroidism leads to neurodevelopmental problems and that timely treatment initiated within the first weeks of life prevents these developmental problems. Since exposure to ICM may lead to prolonged hypothyroidism the goal of thyroid function monitoring after the use

of iodine-based contrast media (ICM) is the prevention of neurodevelopmental delay. However, studies designed to answer the question whether monitoring of thyroid function and the subsequent thyroid hormone supplementation in children exposed to ICM leads to better neurodevelopmental outcome are missing.

A systematic literature search based on the abovementioned did not result in any articles meeting the inclusion criteria. Nine studies were excluded because of missing control groups as defined in the PICO or having a design (and thus population) focused on a different question than the search question. However, these nine studies did report thyroid function monitoring after the use of ICM and are described in table 1. The studies of Gilligan (2021) and Rath (2019) included a non-iodine exposed control group. Gilligan (2021) compared 114 children £ 24 months with either a single ICM enhanced CT (57 exposed cases) or an abdominal ultrasound (57 unexposed cases) and found no differences in TSH levels measured within three months after imaging. Rath (2019) performed a randomized controlled trial comparing 20 preterm infants receiving iodinated contrast to 21 preterm infants receiving only saline to ascertain peripherally inserted central catheter tip position. No differences in thyroid function were found.
Williams (2016) studied 173 preterm infants (<32 weeks) with exposure to either iodinated contrast or topical iodine during caesarian section and reported thyroid dysfunction mainly in the topical exposure group. The remaining six studies all included cardiac patients undergoing either cardiac CT, angiography, or catheterization. Age groups varied from preterm to eight years. Belloni (2018) reported only transient TSH decrease while the other studies reported hypothyroidism in varying frequencies and duration. Reported rates were highest in infants under three months of age (Jick 2018), low-weight and premature infants (Rosenberg 2018) and in case of renal impairment and multiple iodine exposures (Thaker 2017).
Since these studies include variable age groups, different ICMs, and variable follow-up they do not sufficiently answer the search question.

In 2009 Ahmet and coworkers performed a systematic review in order to determine whether neonates exposed to iodinated contrast media are at risk of hypothyroidism (Ahmet, 2009). They included 11 studies, published between 1986-2000. These were older studies not included in our search. These 11 studies included 182 hospitalized neonates (72 term born, 110 preterm born) exposed to iodinated contrast. Six out of 72 (8.2%) exposed term infants were treated for hypothyroidism and 20 out of 110 (18.2%) exposed preterm infants. The authors concluded that hospitalized neonates exposed to ICM are at risk for abnormal thyroid function and hypothyroidism and that premature infants might be at increased risk. However the studies were however highly affected by bias calling for well-controlled studies.

In the various studies the reported prevalence of hypothyroidism after the use of ICM ranges from 1 to 15%. Overall children in the first three months of life seem most at risk of developing thyroid dysfunction after exposure to ICM. More specifically at high risk seem to be premature neonates, low-birth weight neonates and critically ill infants. Also, renal impairment, cardiac disease, and prolonged/frequent exposure to ICM such as during cardiac bypass and dialysis are risk factors.

An important unanswered question is whether infants between 3 months and 3 years are at risk of developing hypothyroidism after exposure to ICM. Also, whether this is dose dependent and what the duration of the hypothyroidism is and whether this would affect neurodevelopment if left untreated.

Most studies focus on the use of intravascular ICM in neonates, but iatrogenic hypothyroidism has also been described after enteral and lymphatic ICM exposure (Putnins, 2020; Cherella, 2018; Lombard, 2009, Ares 2008).

Since enteral ICM is regularly used in (premature) newborns with congenital intestinal diseases, this may lead to a high uptake of iodine in the blood system of this vulnerable patient group, particularly in case of prolonged stasis in children with intestinal obstruction (own observation, manuscript in preparation). Although the causal relationship is not definitive, but with incidental cases of prolonged hypothyroidism after enteral ICM administration having been reported, we advise thyroid function monitoring in preterm infants exposed to intravascular and enteral administration of ICM (Putnins 2020; Lombard, 2009, Ares, 2008). Future studies need to investigate the effect on thyroid function of various modes of administration of ICM, with proper control groups not receiving ICM.

The use of ICM prior to or during pregnancy may also affect neonatal thyroid function. A systematic review on neonatal thyroid function after the use of maternal ICM found a tendency towards an increased risk for hypothyroidism especially in case of higher doses (van Welie 2021). Most ICM are water-soluble and readily cleared from the body. Lipid-based ICM have a delayed excretion. Lipid-based ICM are used for hysterosalpingography but does not seem to affect neonatal thyroid function (Mathews 2023; van Welie 2020).

In March 2022 the FDA issued a drug safety communication recommending thyroid function monitoring of children under three years of age within three weeks of intravascular administration of iodine-based contrast media (FDA, 2022). In a reaction to this recommendation the Pediatric Endocrine Society (PES) and American College of Radiology (ACR) published statements questioning this recommendation due to lack of sufficient evidence (PES 2022). Based on this criticism the FDA issued a revised statement in June 2023 (FDA, 2023). In the revised statement the FDA states "…decisions about thyroid monitoring following administration to children 3 years and younger should be individualized based on each child's risk factors. These risk factors may include prematurity, very low birth weight, and underlying medical conditions affecting thyroid function."

In view of the lack of well-designed studies in this field and to prevent conflicting statements as much as possible, we decided to adopt several of the PES guideline recommendations (PES, 2022).

Screening for primary hypothyroidism consists of a single TSH measurement, included in the guideline. It is important to realize that due to immaturity of the hypothalamic-pituitary axis TSH rise in case of overt hypothyroidism may be delayed or even absent in premature infants, especially in very low birth weight infants (< 32 weeks' gestation and/or < 1500 grams). This means screening with TSH may miss hypothyroidism in these cases. In addition, premature infants have lower thyroid hormone levels than term born infants (transient hypothyroxinemia of prematurity) and critical illness reduces thyroid hormone concentrations, so-called non-thyroidal illness. These factors make it difficult to certify whether exposure to ICM is the actual cause of the hypothyroidism in hospitalized ill infants.

Patient (and their caretakers) values and preferences

Patients, parents/caretakers and health care professionals want to make decisions based on the best available

evidence. A similar case should get equal advice/treatment. The recent FDA advice about monitoring thyroid functioning after iodinated contrast administration makes it necessary to formulate guidelines on whether children in the Netherlands should be monitored. This guideline defines which patients are at increased risk of hypothyroidism after exposure to ICM and provides recommendations on how to apply thyroid monitoring for these populations.

The main benefit of monitoring thyroid functioning is that physicians can identify cases of hypothyroidism that require treatment with daily levothyroxine supplementation to prevent potential brain damage. Monitoring itself involves additional TSH measurements for 2 to 3 weeks after administration of ICM. The populations specified in this guideline are most likely inpatients at neonatology and intensive care wards and are expected to be undergoing frequent blood withdrawals. Blood tests for thyroid monitoring can be combined with other necessary blood tests. The burden of daily levothyroxine supplementation and regular blood withdrawals is considered acceptable in view of the importance of preventing hypothyroxinemia induced brain damage.
In infants and young children pain prevention during blood withdrawal is practiced by the use of local agents such as EMLA or lidocaine and if necessary help of a pedagogical assistant

Costs
Most neonates and infants receiving ICM and at risk for developing prolonged hypothyroidism will most likely be inpatients at neonatology and intensive care wards and are expected to be undergoing frequent blood tests. The costs of an extra blood test are low and may be combined with blood testing for another indication. The costs of levothyroxine supplementation are also low. These relatively low costs are considered acceptable given the importance of preventing hypothyroxinemia-induced brain damage. Since hypothyroxinemia-induced brain damage is associated with significant additional healthcare costs over a longer period, early detection and treatment of cases have the potential to reduce associated health costs.

Acceptance, feasibility and implementation
The monitoring itself requires TSH measurements for 2 to 3 weeks after exposure to ICM, which is currently not standard practice. However, only a small group of children at increased risk of hypothyroidism will require thyroid function monitoring. Early detection of thyroid dysfunction and prevention of hypothyroxinemia-induced brain damage by implementing relatively cheap and easy to administer drugs has clear health benefits. Furthermore, the population at-risk identified in this guideline are often inpatients at neonatology and intensive care wards with frequent blood tests. Thus, for most cases monitoring does not require additional handling. Therefore, the guideline development group does not expect obstructions in terms of acceptance, feasibility and implementation.

The guideline development group advice is to include a reference to this guideline in the radiology report when ICM is used in a child younger than 3 years (since all risk groups defined in this guideline are younger than 3 years).

Rationale of the recommendation: weighing arguments for and against the interventions
Given the importance of thyroid hormone for normal brain development it is necessary to prevent prolonged periods of hypothyroidism in children especially in the first 3 years of life.
To prevent hyperthyroidism in the case of excess iodine exposure the thyroidal Wolff-Chaikoff effect

temporarily downregulates thyroid hormone production. After a few weeks an escape from the Wolff-Chaikoff effect occurs and thyroid hormone production is restored. However, prolonged hypothyroidism may occur when the escape from the Wolff-Chaikoff effect fails. Preterm born infants are particularly vulnerable to the suppressive effects of excess iodine due to immaturity of the thyroid gland and inability to escape from the Wolff-Chaikoff effect.

Overall, there is consensus in the field based on earlier studies that children in the first 3 months of life are most at-risk of developing thyroid dysfunction after exposure to ICM in particular:premature neonates, low-birth weight neonates and critically ill infants. Also, renal impairment, cardiac disease, and prolonged/frequent exposure to ICM such as during cardiac bypass and dialysis pose as risk factors.

It remains unclear whether infants between 3 months and 3 years are at risk of developing prolonged hypothyroidism after exposure to ICM and whether this would affect neurodevelopment if left untreated. Given the long-lasting and debilitating effect of hypothyroxinemia-induced brain damage and the relatively low-cost easy-to-implement treatment, the recommendation is to also consider thyroid function measurement in children with the specified risk factor aged 3 months to 3 years.

## Onderbouwing

### Achtergrond

Iodine is essential for thyroid hormone synthesis, and excess iodine exposure may affect thyroid hormone levels. The use of iodine-based contrast media (ICM) for radiological studies leads to excess iodine exposure. In this context it is important to realize that only free iodide is available for uptake by the thyroid gland. ICM mainly contain organically bound iodine that is excreted in the urine unchanged and will not affect thyroid function. However ICM also contain small amounts of free iodide. This concentration varies between different ICM solutions and is batch-dependent with a longer shelf-life leading to a higher free iodine content (van der Molen 2004).

To prevent hyperthyroidism in the case of such excess iodine exposure the thyroid gland temporarily downregulates thyroid hormone production. This is called the Wolff-Chaikoff effect. Within a few days an escape from the Wolff-Chaikoff effect occurs and thyroid hormone production is usually restored to normal within 2 weeks. However, prolonged hypothyroidism may occur when the escape from the Wolff-Chaikoff effect fails. This has been well described in patients with pre-existing thyroid disease. In the fetal period, the thyroid gland is not mature enough to escape from the Wolff-Chaikoff effect until approximately 36 weeks of gestation. This makes the fetus and (premature) neonate particularly vulnerable to the suppressive effects of excess iodine (Lee, 2015). Various studies have shown that intravascular ICM administration reduces thyroid hormone levels in neonates and causes prolonged hypothyroidism. A systematic review including 11 studies with a total of 182 hospitalized neonates exposed to ICM reported hypothyroidism in 8.2% of term infants and 18.2% of premature infants (Ahmet, 2009).

Brain development is critically dependent on thyroid hormone in the first three years of life and therefore prolonged periods of hypothyroidism in infants and young children should be prevented (van Trotsenburg 2021).

In March 2022 the FDA issued a drug safety communication recommending thyroid function monitoring within 3 weeks of intravascular administration of iodine-based contrast media in all children up to 3 years of life. In a reaction to this recommendation the Pediatric Endocrine Society (PES) and American College of Radiology (ACR) published statements questioning this recommendation due to lack of sufficient evidence and proposed a more individualized approach, identifying patient groups who are most at-risk.

In this part of the guideline we address the question whether routine thyroid function monitoring after the use of ICM in children is necessary.

## Conclusies / Summary of Findings

| | |
|---|---|
| **- GRADE** | No evidence was found regarding the effects of thyroid monitoring in children (<18 years of age) undergoing radiological examinations with intravascular iodine-containing contrast agents on *hypothyroidism*. |

| | |
|---|---|
| **- GRADE** | No evidence was found regarding the effects of thyroid monitoring in children (<18 years of age) undergoing radiological examinations with intravascular iodine-containing contrast agents on *hyperthyroidism*. |

| | |
|---|---|
| **- GRADE** | No evidence was found regarding the effects of thyroid monitoring in children (<18 years of age) undergoing radiological examinations with intravascular iodine-containing contrast agents on *irreversible effects of thyroid dysfunction on neurodevelopment of child*. |

## Samenvatting literatuur

No studies fulfilled our PICO criteria. Therefore, no evidence tables, risk of bias assessment and quality assessment were performed for the studies mentioned in Supplemental Table 1.

## Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the results of thyroid function monitoring after the use of iodinated contrast media in children (<18 years) undergoing radiological examinations?

| | |
|---|---|
| P(atients): | Children (<18 years) undergoing radiological examinations with iodinated contrast media (ICM); |
| I(ntervention): | Monitoring of thyroid function after ICM administration. |
| C(ontrol): | No monitoring of thyroid function after ICM administration. |
| O(utcome): | Hypothyroidism, hyperthyroidism, irreversible effects of thyroid dysfunction on neurological development. |

Relevant outcome measures

The guideline development group considered hypothyroidism and hyperthyroidism as critical outcome measures for decision making; and irreversible effects of thyroid dysfunction on neurodevelopment of children as an important measure for decision making.

A priori, the guideline development group did not define the outcome measures listed above but used the definitions used in the studies.

Per outcome the guideline development group defined the following differences as minimal clinically (patient) important differences:

- Hypothyroidism: RR ≤0.8 or ≥1.25 (dichotomous); 0.5 SD (continuous)
- Hyperthyroidism: RR ≤0.8 or ≥1.25 (dichotomous); 0.5 SD (continuous)
- Irreversible effects of thyroid dysfunction on neurodevelopment of child: RR ≤0.8 or ≥1.25 (dichotomous); 0.5 SD (continuous)

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2000 until 24-07-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 85 hits. Studies were selected based on the following criteria:

- Systematic review, randomized controlled trial or observational research comparing thyroid monitoring to no monitoring in children receiving intravascular iodine-containing contrast.
- Children (<18 years) who underwent radiological examination with iodine-containing contrast media (ICM);
- At least one of the outcome measures was described: hypothyroidism, hyperthyroidism.
- Full-text English language publication.

12 studies were initially selected based on title and abstract screening. After reading the full text, all studies were excluded (see the table with reasons for exclusion under the tab Methods).

Results
Since no studies fulfilled the PICO criteria it was not possible to perform a systematic analysis of the literature. Nine studies did have the correct patient population and performed thyroid function monitoring after the use of iodine-containing contrast. These studies are briefly described in Supplemental Table 1. Since these studies include variable age groups, variable iodine-containing contrast substances and variable follow-up they do not answer the search question, and no quality of evidence analysis or evidence tables were made.

## Verantwoording

Laatst beoordeeld : 01-12-2024

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

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