Prevention of Contrast Nephropathy

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Abstract

Contrast nephropathy is a common cause of iatrogenic acute renal failure. Its incidence rises with the growing use of intra-arterial radiocontrast in older patients for diagnostic and interventional procedures. Aim of the present systematic review is to provide evidence based recommendations for the prevention of contrast induced nephrotoxicity.

Nephrotoxicity is related to osmolality, dose and route of the contrast agent and only occurs in synergy with other factors, such as previous renal impairment, cardiovascular disease and the use of certain drugs. Contrast nephropathy has impact on morbidity and mortality. Pathophysiological mechanisms are intrarenal vasoconstriction, leading to medullary ischemia, direct cytotoxicity, oxidative tissue damage and apoptosis. Several measures are of proven benefit in patients at risk. Among them are the use of low osmolal contrast, discontinuation of potentially nephrotoxic drugs, pre-hydration, especially with isotonic sodium-bicarbonate, N-acetylcysteine, theophylline and high dose ascorbic acid. In patients with severe cardiac and renal dysfunction undergoing cardiac interventions, periprocedural hemofiltration may be considered.

Samenvatting

Contrast nephropathie is een veel voorkomende oorzaak van iatrogene acute nierinsufficientie. Met het toenemende gebruik van intra-arterieel radiocontrast bij diagnostische- en interventieradiologie stijgt de incidentie. Doel van dit systematische overzicht is om op klinisch bewijs gebaseerde aanbevelingen te geven voor de preventie van contrast nefropathie.

Nephrotoxiciteit is gerelateerd aan de osmolariteit, dosis en toedieningsweg van het radiocontrast, en komt alleen voor als er tevens sprake is van andere factoren zoals een bestaande nierfunctiestoornis, hart- en vaatlijden. Door een interactie met deze factoren heeft contrast nefropathie invloed op morbiditeit en mortaliteit. Pathofysiologische mechanismen zijn intrarenale vasoconstrictie, waardoor medullaire ischemie ontstaat, directe cytotoxiciteit,

oxydatieve weefselschade en apoptose. Van verschillende maatregelen is de effectiviteit bij risico-patiënten aangetoond. Deze zijn het gebruik van laag-osmolair contrast, het staken van potentieel nephrotoxische medicatie, prehydratie, met name met isotoon natrium bicarbonaat, N-acetylcysteïne, theophylline en een hoge dosering ascorbinezuur. Bij patiënten met een ernstige cardiale en renale insufficiëntie die een cardiale interventie ondergaan kan overwogen worden om rondom de ingreep te hemofiltreren.

Abbreviations

CN	contrast-induced nephropathy
LO-CM	low-osmolal contrast medium
HO-CM	high-osmolal contrast medium
RCT	randomized controlled trial
NAC	N-acetylcysteine
ACE	angiotensin converting enzyme
NSAID's	non-steroid anti-inflammatory drugs
GFR	glomerular filtration rate
cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanine monophosphate
ET	endothelin

Summary recommendations for the prevention of contrast nephropathy (CN) in patients at risk

1. Determine whether the patient is at risk (Table 2). If so, take specific measures to reduce the risk of CN (Grade A).
2. Consider alternative imaging techniques, which do not require the use of intravascular iodinated radiocontrast.
3. Use low-osmolar contrast (about 780 mosm/kg) (Grade A). Iso-osmolal contrast (280 mosm/kg) is less nephrotoxic than low-osmolal contrast (Grade B). Use the lowest possible contrast volume (Grade C).
4. Discontinue potentially nephrotoxic drugs for 24 hours before and after the contrast infusion, if feasible (Table 2). ACE inhibitors can be continued if hydration is adequate. They are protective (Grade C). Stop metformin after contrast administration for at least 2 days until deterioration of renal function is excluded (Grade D).
5. Make sure that the patient is well hydrated. Administer at least a or b:
    a. Sodium bicarbonate (90 ml Sodium Bicarbonate 8.4% added to 500 ml Glucose 5%), 3 ml/kg/h for one hour before and 1 ml/kg/h for six hours after the contrast (Grade B), or
    b. NaCl 0.9 % for 12 h before until 12 h after the contrast (Grade B).

    The sodium bicarbonate regime protects better than the NaCl 0.9 % regime (Grade B). NaCl 0.9 % protects better than NaCl 0.45%.
6. Stop loop-diuretics, mannitol and dopamine (Grade C). If they have to be administered for other reasons, hydrate rigorously, because hypovolemia may be present.
7. In addition to hydration, use specific medication (a, b or c),
    a. Administer N-acetylcystein (NAC) 600 mg orally twice daily on the day before and on the day of the intervention (Grade A). A double dose of NAC (1200 mg) in the same regimen may be more effective (Grade B), but is possibly less tolerated. Use in case of urgent interventions, intravenous NAC, 150 mg/kg in 500 ml N-saline over 30 min before, followed by 50 mg/kg in 500 ml over 4 h (Grade C). The latter regimen is, however, associated with a large volume load.
    b. Administer aminophylline 250 mg (theophylline 200 mg) slowly i.v. 30 min before the intervention in addition to hydration, especially in case of acute interventions (Grade A).
    c. Administer oral ascorbic acid, 3 g at least 2 h before followed by 2 g the night and the morning after radiocontrast administration (Grade B).
8. Correct low plasma magnesium (Grade D).
9. The use of the following medication in the prevention of CN is not recommended:
    a. Calcium-channel blockers. They protect against contrast toxicity (Grade C), but the evidence is small. There is more robust evidence for other interventions.
    c. Fenoldopam (Grade C) and atrial natriuretic peptide (ANP). They do not reduce the incidence of CN.
    d. Mixed endothelin$_{A \text{ and } B}$ receptor antagonists. Drugs with this action may exacerbate CN and should not be used with contrast (Grade B).
10. Prophylactic hemofiltration reduces in-hospital and cumulative one-year mortality in patients with renal dysfunction undergoing cardiac catheterisation, specifically in the subgroup of patients with baseline creatinine greater than 334 µmol/L. Apply hemofiltration in patients with severe cardiac and renal dysfunction (Grade B). Do not use prophylactic hemodialysis (Grade B).

    - *Until now, neither NAC, nor theophylline, ascorbic acid, hemofiltration or sodium bicarbonate hydration are compared to each other.*

Samenvatting van de aanbevelingen voor de preventie van contrast nefropathie (CN) bij risico patiënten

1. Specifieke maatregelen verminderen de kans op CN bij risico patiënten (Niveau A).
2. Overweeg bij risico patiënten beeldvorming waarbij geen intravasculair jodiumhoudend röntgencontrast wordt toegediend.
3. Gebruik laag-osmolair contrast (780 mosm/kg) (Niveau A). Iso-osmolair contrast (280 mosm/kg) is nog minder nefrotoxisich dan laag-osmolair contrast (Niveau B). Gebruik het laagst mogelijke contrast volume (Niveau C).
4. Stop potentieel nefrotoxische medicatie vanaf 24 u voor tot 24 u na de toediening van röntgencontrast (Tabel 2). Bij goede hydratie kunnen ACE remmers gecontinueerd worden. Zij zijn protectief (Niveau C). Stop metformin na de toediening van röntgencontrast gedurende tenminste twee dagen tot achteruitgang van de nierfunctie is uitgesloten (Niveau D).
5. Zorg voor een goede intravasculaire vullingstoestand. Geef tenminste a of b
    a. Natrium bicarbonaat (90 ml natrium bicarbonaat 8.4 % toegevoegd aan 500 ml glucose 5 %), 3 ml/kg in het uur voor de toediening van röntgencontrast gevolgd door 1 ml /kg/u gedurende 6 u na het contrast (Niveau B), *of*
    b. NaCl 0.9%, 1 ml/kg/u vanaf 12 u voor tot 12 u na het röntgencontrast (Niveau B).

   Het natrium bicarbonaat regime geeft een betere bescherming dan hydratie met NaCl 0.9 % (Niveau B) en NaCl 0.9% beschermt beter dan NaCl 0.45 % (Niveau B).
6. Stop lisdiuretica, mannitol en dopamine (Niveau C). Als zij om andere redenen noodzakelijk zijn, zorg dan voor een goede vullingstoestand, omdat er sprake kan zijn van hypovolemie.
7. Dien naast vocht specifieke medicatie toe (a, b of c):
    a. Geef N-acetylcysteine (NAC) 600 mg per os twee maal daags op de dag voor en de dag van het röntgencontrast (Niveau A). Een dubbele dosering NAC (1200 mg) is wellicht effectiever (Niveau B), maar wordt minder goed verdragen. Geef in geval van een spoedinterventie NAC 150 mg/kg in 500 ml NaCl 0.9 % in 30 min voor de röntgencontrast toediening, gevolgd door 50 ml/kg in 500 ml in 4 u na het contrast (Niveau C). Het laatste regime geeft een grote volume belasting.
    b. Geef naast vocht aminophylline 250 mg langzaam intraveneus (overeenkomend met theophylline 200 mg) 30 min voor de toediening van röntgencontrast (Niveau A), in het bijzonder in geval van een spoedinterventie.
    c. Geef ascorbinezuur per os, 3 g tenminste 2 u voor, gevolgd door 2 g ‘s avond en ‘s ochtends na de toediening van röntgencontrast (Niveau B).
8. Corrigeer een laag plasma magnesium (Niveau D).
9. Het preventieve gebruik van de volgende medicatie wordt niet geadviseerd:
    a. Calciumantagonisten. Zij beschermen tegen contrast nefropathie (Niveau C), maar het bewijs is zwak. Voor andere interventies is een sterker bewijs.
    b. Fenoldopam (Niveau C) en atriale natiuretische factor (Niveau B). Zij geven geen bescherming.
    c. Gemengde endotheline A en B remmers. Middelen met deze werking kunnen de toxiciteit van röntgencontrast versterken en moeten niet in combinatie met contrast worden gebruikt (Niveau B).
10. Profylactische hemofiltratie verhoogt de ziekenhuis- en de 1-jaarsoverleving bij patiënten met nierinsufficiëntie die een hartcatheterisatie ondergaan, met name in de subgroep met een plasma creatinine van meer dan 334 µmol/L. Pas profylactische hemofiltratie toe bij patiënten met een ernstige gecombineerde hart en nierinsufficiëntie (Niveau B).

- *Tot op heden zijn er geen studies die het effect van NAC, theophylline, ascorbinezuur, natrium bicarbonaat en hemofiltratie onderling vergelijken.*

Introduction

Contrast nephropathy (CN) is the third most common cause of iatrogenic acute renal failure. Nephrotoxicity of radiocontrast depends on the type, dose and route of the contrast agent used and only occurs in synergy with other factors [1,2]. CN is rare in patients with normal renal function, but its incidence rises with the growing use of intra-arterial contrast in diagnostic and interventional procedures in older patients with premorbid renal impairment and cardiovascular disease [2-6]. In this population, CN is associated with increased length of stay in the hospital, temporary renal replacement therapy, or loss of residual renal function, especially in those with pre-existing renal insufficiency. In some patients, CN may even contribute to mortality [2,6-9]. The exact mechanism of renal impairment has not been fully elucidated yet, but clinical and experimental data show that afferent vasoconstriction, medullary ischemia, direct cytotoxicity, oxidative tissue damage and apoptosis are involved [10-17]. In addition, renal insufficiency after radiocontrast procedures with catheterisation of the aorta may be caused by cholesterol embolism or atheroembolism from the aorta [18-21]. The renal failure can be acute, but a progressive loss of function may occur over weeks. Renal failure is typically associated with one or more of the following symptoms: hypereosinophilia, neurological symptoms, hypertension, pain in the back, leg or abdomen, trash toes or *livedo reticularis* in the lower part of the body due to microembolism of cerebral, gastrointestinal, pancreatic, leg or skin vessels. Dialysis is required in up to 60 % of the cases and one year mortality is high, reported rates are 21-87% [18].

Aim of the present review is to provide evidence based recommendations for the prevention of CN.

Methods

We performed a MEDLINE search up to 1st of August 2004 for clinical trials, observational studies and reviews limited to the English language. The following key words were used: 'contrast', 'nephropathy', 'contrast media', 'adverse events' and their combinations. Concluding recommendations are based on the NVIC gradation system for Evidence-based Guidelines. Studies are categorized according to Levels, ranging from I to V and the Grade of recommendation is based on the number and level of the studies [22]. Criteria for the qualification 'Level I', a large randomised controlled trial (RCT) and 'Level II', a small RCT, are not well settled. In the present review, fifty patients per group were taken as a cut-off.

Definition

For research purpose, CN is defined as an acute impairment of renal function manifested by a 25 % increase in serum creatinine concentration or an absolute increase of 0.5 mg/dl (44.2 μmol/l) in the absence of other causes [23,24]. The serum creatinine typically peaks three to five days after contrast exposure and usually returns to the baseline value within one to three weeks.

Risk factors and incidence

The risk for developing CN depends on the premorbid condition of the patient and the type, dose and route of the contrast. CN is a virtual problem in a healthy patient with normal renal function. However, in clinical conditions associated with a reduced effective circulatory volume, pre-existing renal insufficiency, diabetes mellitus, vascular disease, advanced age and heart failure the incidence of CN is high, it is reported in up to 15-50 % of the patients [1,5,8,7,25,26]. In these conditions, the vasoconstricting and toxic effects of the contrast medium are exaggerated as a result of the afferent vasoconstriction associated with a reduced effective circulatory volume. The osmotic diuresis due to the contrast may further aggravate vascular contraction. In addition, patients with vascular disease have an impaired endothelial derived vasodilatation, a necessary compensation to maintain renal perfusion under these conditions. In pre-existing renal insufficiency the reduced number of functioning glomeruli receive the entire contrast load. In critically ill and older patients, anti-oxidant defence may be decreased [15]. Furthermore, the concomitant use of several drugs increases the

nephrotoxicity of the contrast, especially drugs that cause renal damage by the same pathways as radiocontrast: intrarenal vasoconstriction, generation of oxygen-derived free radicals and induction of apoptosis [27-29] (see below). Increased renal toxicity with the use of these drugs may be related to the combination of the drug, the contrast, and the associated disease, such as sepsis or dehydration. Finally, the risk for developing CN is increased in patients with multiple myeloma. In a review of seven retrospective studies enclosing 476 patients with myeloma receiving contrast, the prevalence of ARF was only 0.6 – 1.25 % [30]. In a recent study from India involving 204 cases, CN occurred in 2% [31]. The risk for renal involvement in multiple myeloma is related to hypercalcemia, dehydration, concomitant use of nephrotoxic drugs, infection and Bence Jones proteinuria.

Risk factors for the development of cholesterol embolism are atherosclerosis of the aorta en renal insufficiency [19], mobile atheromatous lesions and a high CRP [20,21] and hypercholesterolemia [18]. Unstable plaques are characterized by echolucency, inhomogenity, absence of calcifications, mobility and spontaneous contrast in the aorta [18]. These risk factors have a poor specificity, since the incidence of renal failure due to cholesterol embolism after contrast procedures is rare. A rate of 1.4 % is reported in a prospective study [20].

Risk factors related to the type, route and volume of the contrast are discussed below.

The incidence of CN induced by low-osmolal contrast medium (LO-CM) is less than 2 % in the general population. In patients at risk (Table 2) the incidence increases along with the number of risk factors to more than 20 % in patients with more than two risk factors [1] and may amount to 50 % among patients with severe diabetic nephropathy [25,26] or heart failure despite hydration and the use of low osmolal contrast medium.

It may be clear that CN is not an isolated problem. Despite the consensus definition, mentioning the 'absence of other causes', ARF after contrast generally occurs in a kidney receiving hit on hit on hit. It may therefore be clear that many critically ill patients have several risk factors for the development of contrast induced nephropathy. Especially in this population, the aggravation of renal insufficiency may contribute to mortality. To lower the damage, specific measures have to be taken.

In patient is at risk (Table 2) specific measures reduce the risk of CN (Grade A)

Preventive measures

The primary and crucial step in the prevention of CN is to determine whether the patient is at risk (Table 2). If not, no specific measures have to be taken. If the patient is at risk, consider alternative imaging techniques, which do not require the use of iodinated contrast medium. If there are no alternatives, take specific measures to protect against CN. There is no preven benefit of specific measure for the prevention of cholesterol embolism. In contrast to expectation, the incidence of cholesterol embolism after cardiac catheterisation was not lower with the brachial than with the femoral approach [20].

The contrast: type, dose and route

Toxicity of the contrast medium (CM) is related to osmolality [16], dose and route of administration. Osmolality of the first generation *high*-osmolal (HO) ionic monomers is extremely high (1500-1800 mosm/kg). The so-called *low*-osmolal (LO) agents still have an osmolality higher than plasma, about 780 mosm/kg, and only the third generation dimers are *iso*-osmolal to plasma [32]. In a meta-analysis [33] and a RCT in 1196 patients undergoing non-emergent diagnostic cardiac angiography (*level I*) [34] it was shown that, compared to HO-CM, LO-CM reduces the risk of CN in the patients with previous renal dysfunction, serum creatinine greater than 1.5 mg/dl (136 µmol/l) receiving intra-arterial contrast, but not if renal function is normal, nor if the contrast is administered intravenously. In a recent RCT in 129 patients with diabetes mellitus and renal dysfunction (serum creatinine 1.5 to 3.5 mg/dl (133-317 µmol/l) undergoing coronary or aortofemoral angiography, the incidence of contrast nephropathy was lower, when iso-osmolal contrast (280 mosm/kg) was used rather

than a second generation LO-CM (780 mosm/kg) [35] (*Level I*). In a RCT in 21 patients with severely impaired renal function undergoing peripheral angiography, the use of gadolinium showed no benefit over iohexol with respect to preventing GFR reduction *(Level II)* [36]

In most studies, use of a higher contrast volume is associated with more renal toxicity [1,7,8,25,37-39] in some, dose was not a risk factor [40]. In several studies, the risk of CN is higher after intra-arterial than after contrast administration by the intravenous route [1,33,34].

> *Use low-osmolar contrast (grade A). Iso-osmolal contrast may be less nephrotoxic than low-osmolal contrast (Grade B). Use the lowest possible contrast volume (Grade C).*

Concomitant use of potentially nephrotoxic drugs

It should be considered, whether potentially nephrotoxic drugs (Table 2) can be discontinued, if possible for at least 24 hours before and after the intervention. These drugs may augment the toxic effects of the contrast by their effects on renal hemodynamics (e.g. non-steroid antiinflammatoy drugs, NSAID's) or by mediating oxygen radical damage (e.g. aminoglycosides). Most feared are the NSAID's. They inhibit the synthesis of prostaglandines, mediators of compensatory afferent and medullary vasodilatation. [12,27,28,41]. Other potentially nephrotoxic drugs that increase the risk of CN are summarized in Table 2. In contrast to what is often stated, angiotensin concerting enzyme (ACE) inhibitors do not increase the incidence of CN if hydration is guaranteed. They are even protective [42].

In patients taking metformin, life threatening lactic acidosis is reported following the use of radiocontrast. The reason is that metformin accumulates, if renal function deteriorates. The risk of lactic acidosis seems to occur if and when renal function is abnormal prior to the administration of radiocontrast, and not with normal renal function [43].

> *Iif feasible, discontinue potentially nephrotoxic drugs for 24 hours before and after contrast infusion (Table 2).*
> *ACE inhibitors are allowed to be continued if hydration is adequate. They are protective (Grade C).*
> *Stop metformin after contrast administration for at least 2 days until the deterioration of renal function is excluded (Grade D).*

Pre-hydration (see table 3)

From a theoretical point of view, pre-hydration of patients may be beneficial by correction of plasma volume depletion. Volume depletion leads to renal vasoconstriction and active sodium reabsorption, an oxygen demanding process. Volume expansion down-regulates tubuloglomerular feedback and decreases activity of the renin-angiotenin system, endothelin and other intrarenal vasoconstrictors [44]. Volume expansion also dilutes the CM, minimizes tubular hyperosmolality and prevents the consequences of osmotic diuresis. In a RCT in 53 patients scheduled for cardiac catheterisation, the incidence of CN was significantly lower in the patients receiving normal saline 1 ml/kg/h for 24 hours beginning 12 h before contrast (1 out of 27) than in the control group with unrestricted oral intake (9 out of 29) [45] (*Level II*). In a recent small RCT in 39 patients with normal renal function receiving intravenous or intra-arterial contrast, intravenous saline hydration for 12 h before and after the contrast reduced GFR significantly less than an intravenous saline bolus of 300 ml during the contrast and unrestricted oral intake thereafter (*Level II)*. Prolonged hydration was associated with less activation of the renin-angiotensin system and an increased sodium excretion [46] (*Level II*). In a large RCT evaluating 1383 patients scheduled for elective or emergency coronary angioplasty, isotonic saline hydration was superior to half-isotonic hydration in the prevention of CN [7] (*Level I*). Three predefined subgroups benefited in particular from isotonic saline hydration: women, patients with diabetes and patients receiving 250 ml or more of radiocontrast. Two RCT's in 60 respectively 78 patients with chronic renal insufficiency showed that saline hydration alone was as effective or even better than the additional

administration of low dose dopamine [47] (*Level II*), hypertonic mannitol or furosemide [48] (*level II*).

In a recent RCT in 119 patients with stable chronic renal dysfunction, hydration with sodium bicarbonate (90 ml Na-bicarbonate 8.4% added to 500 ml glucose 5%), 3 ml/kg/h for six hours before and 1 ml/kg/h for six hours after the administration of LO-CM, was superior to hydration with normal saline. The incidence of CN was 2 % in the bicarbonate-treated patients and 17 % in the patients receiving saline (*Level I*) [51]. The investigators postulated that the bicarbonate protected the kidney from free radical damage generated in the acid milieu of the renal medulla.

> *Make sure that the patient is well hydrated. Intravenous hydration protects better against contrast nephrotoxicity than unrestricted oral intake (Grade C). Intravenous hydration for 12h before and 12h after contrast protects better than hydration during the procedure only (Grade C). It is recommended to administer either isotonic bicarbonate, 3 ml/kg/h for one hour before and 1 ml/kg/h for six hours after the contrast, or NaCl 0.9 % for 12 h before until 12 h after the contrast. The sodium bicarbonate regime protects better than the normal saline regime (Grade B) and NaCl 0.9 % protects better than NaCl 0.45% (Grade B). Isotonic sodium bicarbonate can be prepared by adding 90 ml sodium bicarbonate 8.4% to 500 ml glucose 5%.*

Specific medication

N-acetylcysteine (NAC).

Of the ten RCT's published as a full paper on the effect of oral NAC in addition to periprocedural N-saline hydration on the prevention of CN in patients with chronic renal insufficiency, four show a significant protection against the development of CN [39,52-54] and six showed no benefit [8,37,55-58]. All used LO-CM and included patients with chronic renal insufficiency; most included only elective procedures. Details of the studies are presented in Table 4. NAC was generally administered the day before and the day after contrast in a 600 mg oral dose twice daily. In two studies (one positive and one negative) preprocedural NAC was administered in a single dose [39,56]. One RCT used intravenous NAC, 150 mg/kg in 500 ml NaCl 0.9% over 30 min before, followed by 50 mg/kg in 500 ml over 4 h [59]. There are three meta-analyses, all three included the first seven trials with oral NAC and the RCT with intravenous NAC in their analysis [60-62]. One meta-analysis additionally included four studies in a sensitivity analysis that were only published in abstract form at the time of the analysis [62]. One of these studies is now published as a full paper (8). All three meta-analyses conclude that, NAC in addition to saline hydration significantly reduces the risk for CN in patients with chronic renal insufficiency. After the first two meta-analyses three negative RCT's and after the last meta-analysis two additional negative RCT's with NAC appeared [8,57,58]. Nevertheless, if we pool all data from the RCT's published until now and reported in Table II, CN occurred in 51/581 NAC patients and in 94/592 placebo patients, yielding a risk of developing CN in the placebo patients of 0.16 (odds 0.17) and of 0.09 (odds 0.10) in the patients receiving NAC. The relative risk for developing CN when NAC is used is 0.53 (95% CI 0.40 - 0.76).

In an additional RCT in patients undergoing coronary or peripheral angiography, a double dose of NAC in addition to NaCl 0.45% hydration was more effective than the standard dose of 600 mg twice daily [63]. In contrast to this result, in the study using the largest dose, 4 times 1500 mg, NAC had no effect [8]. Although there are differences between the different trials in hydration regime, dose of NAC, baseline creatinine, and volume of contrast, it does not appear that the conflicting results can be attributed to these factors.

Side effects of NAC are few. Oral NAC may cause gastro-intestinal side effects, such as nausea and vomiting, especially in the higher dose [8]. The volume loading associated with intravenous NAC as proposed in the rapid regime may lead to congestive heart failure [59].

Mechanism. NAC has been used successfully in ischemia reperfusion injury of the heart, kidney, lung and liver. In animal studies, NAC reduced renal dysfunction and outer

medullary vasoconstriction after ischemia. This effect seemed to depend on scavenging of peroxynitrite and on the presence of NO [64]. However, oxidant stress as measured with urinary isoprostanes was not increased after contrast exposure in a human study. In this study, insight was provided into the possible mechanisms of renoprotection of NAC in patients. In the placebo patients, urinary NO_x decreased after contrast, whereas no decrease was observed in the NAC-treated patients [65]. It has been shown *in vitro* that NAC can induce endothelial NO synthetase expression. Futhermore, NAC may potentiate the vasodilating effects of NO by binding to it and forming S-nitrosothiol, a more stable vasodilator. NAC may inhibit cell death after ischemia-reperfusion and promotes pathways that lead to repair and survival during oxidative stress. The decrease in serum creatinine as observed in the different studies with NAC may therefore be attributed to its anti-oxidant effect, but also to its vasodilator effect mediated by stabilizing endothelial-derived NO.

It should, however, be noted that in five of the RCT's serum creatinine decreased in the NAC group [39,52-54,59]. This could be the result of an improvement of renal function. Another explanation may be that NAC has a direct effect on creatinine concentration, independent of glomerular filtration [66]. In healthy volunteers, serum creatinine and urea concentration decreased significantly four hours after a two-day's course or oral NAC, while cystatine-C, another marker of GFR remained unchanged. If this observation is confirmed, the protective effect of NAC on kidney damage may be questioned.

> *In addition to hydration, administer N-acetylcysteine (NAC) 600 mg orally twice daily on the day before and on the day of the intervention (grade A). A double dose of NAC (1200 mg) in the same regimen may be more effective (grade B), but is possibly less tolerated Use in case of urgent interventions, intravenous NAC, 150 mg/kg in 500 ml N-saline over 30 min before, followed by 50 mg/kg in 500 ml over 4 h (Grade C). The latter regimen is, however, associated with a large volume load.*

Theophylline. There are eight RCT's on the effect of oral aminophylline or theophylline in patients with chronic renal insufficiency on the prevention of CN. An aminophylline dose of 250 mg corresponds to theophylline 200 mg. The drug was generally given once as a short infusion 30 minutes before the intervention. Six out of these eight studies show a significant protection against the development of CN [38,67-71] and two show no benefit [72,73]. Some of the studies are of older date, before the consensus definition, and the primary endpoint is therefore less homogenous. However, all measured serum creatinine and/or (additional) clearance at least 48 h after the procedure. Of the five studies using LO-CM, three were positive (see Table 4). One additional study also compared HO-CM to LO-CM, in the HO-CM group aminophylline was protective both at 24 and 48 h, while in the LO-CM group GFR only decreased after 24 h and not after 48, the decrease after 24 h was prevented by theophylline. Of the four studies applying periprocedural saline hydration, two were positive. In two additional positive studies using LO-CM, hydration was adjusted to clinical findings and an intake of at least 2 L/day was advised. In the cardiological patients, volume was adjusted to clinical examination, x-ray and central venous pressure [38,71]. In a small study of patients with severe renal insufficiency who could not be pre-hydrated, theophylline prevented CM-induced ARF better than NAC [74]. Until now, this study has only been presented in abstract form.

Mechanism. The protective effect of theophylline might be attributed to its action as a non-selective adenosine receptor blocker, but also to its non-selective phosphodiesterase inhibitor effect. The effect of non-selective adenosine blockade in the kidney is complex (see pathophysology). Theophylline decreases urinary adenosine excretion after the administration of contrast [68]. Theophylline prevents the sustained decrease in renal blood flow and GFR after CM infection in animals with renal dysfunction, but also the short increase that occurs after CM in dogs with normal renal function [12,75]. The protective effect of theophylline is to be attributed to adenosine-1 receptor antagonism (75,76), but possibly also to adenosine-3 antagonism (77,78). Furthermore, phosphodiesterase inhibition preserves intracellular cAMP

and cGMP, preventing vasoconstriction. Finally, cAMP prevented the caspase-dependent apoptotic renal cell damage caused by contrast media *in vitro* [79].

> *In addition to hydration, administer aminophylline 250 mg (theophylline 200 m) slowly i.v. 30 min before the intervention, especially in case of acute interventions or when the possibility of prehydration is limited (grade A)*

Ascorbic acid.
Oxidative injury is one of the proposed mechanisms of toxicity due to radiocontrast. In a RCT in 231 patients with renal insufficiency (creatinine ≥ 106 μmol/l) undergoing coronary angiography and/or intervention oral administration of the anti-oxidant ascorbic acid, 3 g at least 2 h before, followed by 2 g in the night and the morning after radiocontrast administration reduced the incidence of contrast nephropathy from 20 % to 9 % (odds ratio 0.38, 95 % confidence interval 0.17 to 0.85) (*Level I)* [80].

Calcium-channel blockers. Calcium channel blockers prevent the decline in renal plasma flow and GFR after radiocontrast injection in animals [81] and patients [11]. In addition to inhibition of vasoconstriction, calcium channel blockers may prevent intracellular calcium overload after ischemic or toxic injury, decrease free radical formation and control immune response [82]. Despite this, results of clinical trials are conflicting. In a small RCT including 35 patients a three-day pre-treatment with nitrendipine, 20 mg per day orally, preserved glomerular filtration, whereas control patients showed a 27% decline [83]. In another RCT including 85 patients, a beneficial effect of a single dose of 10 mg nifedipine could not be shown [84].

> *Calcium-channel blockers protect against contrast toxicity (level II). The evidence is too small to recommend its use for prevention. There is more robust evidence for other interventions.*

Furosemide and mannitol (see also Table 3). There is no evidence to support a protective role of loop-diuretics or mannitol in the prevention of CN. Most investigators showed no benefit or sometimes even worse results. In a RCT including 78 patients, saline plus furosemide and saline plus mannitol were less effective in preventing CN than saline alone [48] *(Level II)*. In a RCT including 98 patients undergoing coronary angiography, forced diuresis with crystalloids, furosemide, mannitol and low dose dopamine was equivalent to forced diuresis alone. In the overall population of this study, forced diuresis with or without the additional above regimen provided a modest benefit against CN, if a diuresis of more than 150 ml/h could be achieved (rate of contrast nephropathy 22 vs. 46 %, p = 0.03). In a RCT including 66 patients with mild to moderate renal dysfunction and or diabetes mellitus undergoing coronary angiography, forced diuresis with intravenous crystalloids, furosemide, mannitol (if pulmonary artery occlusion pressure was < 20 mm Hg) and low dose dopamine was not more effective than hydration alone in the prevention of CN [49].

Mechanism. The adverse effects of furosemide might be attributed to its vasodilatory effect in the renal cortex causing redistribution of blood flow with steal from the medulla. Furthermore, sustained diuresis under furosemide might elicit vascular contraction and loss of magnesium. Both vascular contraction and low magnesium are known to be associated with increased contrast-induced nefrotoxicity [12,14]. If furosemide is indicated for other reasons, vascular contraction should be avoided rigorously. Mannitol might have adverse effects by increasing osmolarity.

> *Stop loop-diuretics and mannitol (Grade C) If diuretics have to be administered for other reasons, hydrate rigorously, because hypovolemia may be present.*

Dopamine. In a RCT in 30 patients with mild to moderate renal failure undergoing coronary angiography, dopamine (D) increased renal blood flow, but had no advantage over hydration

with NaCl 0,45 % in the protection against CN *(Level II)* [85]. In another small study, dopamine or mannitol reduced the risk of CN in non-diabetics but increased its incidence in patients with diabetes mellitus [26]. In a RCT including a comparable population of 66 patients, there was no advantage of dopamine in addition to 0.9 % hydration over hydration alone [47]. Dopamine did also not protect against CN in a RCT comparing hydration to aminophylline or dopamine in addition to hydration (Table 4) [72]. In a subgroup of patients with peripheral vascular disease of the latter study, the increase in serum creatinine was even higher in the dopamine group [47]. After development of CN, dopamine had a deleterious effect on recovery [72]. This may be related to the nonspecific nature of dopamine, stimulating D_1 and D_2 receptors and in a higher dose, additionally α and β receptors.

> *Stop low dose dopamine before contrast administration (Grade C). If dopamine has to be administered for other reasons, prevent dehydration rigorously, because hypovolemia may be present.*

Fenoldopam mesylaat. Fenoldopam, a selective D_1 receptor agonist, promotes renal vasodilation. In volume depleted dogs, low dose fenoldopam amplified the increase of vasodilation following HO-CM injection, and blunted the subsequent vasoconstrictor response and the fall in GFR [86]. In a RCT in 96 patients undergoing contrast angiography, fenoldopam non-significantly reduced the incidence of CN from 41 to 21 % [87]. Another RCT in 123 patients scheduled for cardiovascular procedures with renal dysfunction, comparing NaCl 0.45%, fenoldopam in addition to saline, and NAC plus saline showed no superiority of any of the interventions [55]. In non-randomized controlled studies, the incidence of CN was lower in the fenoldopam group compared to contemporary or historical controls [87,88].

> *The addition of fenoldopam is not better than saline hydration alone in the prevention of CN. The intervention is not recommended (grade C).*

Atrial natriuretic peptide (ANP). In a RCT evaluation 247 patients with pre-existing chronic renal failure, with or without diabetes mellitus, intravenous ANP before and during a radiocontrast study in addition to 0.45 % NaCl hydration did not reduce the incidence of CN compared to hydration alone *(level I)* 90].

> *The addition of ANP to saline hydration does not reduce the incidence of CN. The intervention is not recommended (grade B)*

ACE inhibition. Activation of the renin-angiotensin system seems to be involved in CN. A single dose of captopril partially prevented the fall in renal plasma flow and GFR following HO-CM in patients with renal dysfunction undergoing water diuresis [11]. In a RCT in 71 patients with diabetes mellitus undergoing coronary angiography, the use of captopril 25 mg thrice a day for three days starting one hour before angiography reduced the risk of development of CN by 79 % (*Level II*) [42].

> *The use of ACE inhibitors protect against CN (Level II). There is no reason to stop an ACE inhibitor in patients receiving contrast if adequate hydration is guaranteed (Grade C).*

Endothelin-receptor antagonism. Following the injection of CM, endothelin (ET) is released [91-93]. Urinary ET/creatinine ratio increased in patients with renal dysfunction, but not in those with normal renal function [94]. Pretreatment of rats with an ET_A receptor antagonist did not affect the transient fall in outer medullary blood flow after contrast, but the fall in outer medullary PO_2 was diminished [95]. Contrary to expectation, in a RCT in 158 patients with chronic renal dysfunction, mixed $ET_{A\text{ and }B}$ receptor antagonism in combination with saline hydration exacerbated contrast induced nephrotoxicity compared to hydration alone [96]. This deleterious effect may be explained by the finding that plasma ET concentrations

were higher after the administration of the non-selective ET antagonist than in the placebo group and remained higher than placebo after 24 hours, an effect mediated by antagonism of the ET_B clearance receptor. Since the ET antagonist was administered by a 12-h intravenous infusion only, the high plasma ET concentration lasted while the protective effect of ET_A receptor antagonism had weaned off and this high ET concentration might have contributed to renal toxicity in the presence of contrast [97].

> *Mixed $ET_{A\ and\ B}$ receptor antagonism may exacerbate contrast induced nephrotoxicity (Level I). The drug should not be used with contrast (Grade B)*

Other measures. Magnesium has anti-oxidant properties [98]. In patients with low plasma magnesium more nephropathy is seen after contrast than in patients with normal plasma magnesium *(Level III)* [14].

> *Correct low plasma magnesium (Grade D).*

Prophylactic hemofiltration. Radiocontrast can be removed by extracorporeal treatment. In a randomized trial, hemodiafiltration and high-flux hemodialysis appeared to be more effective with respect to clearance than low-flux hemodialysis and hemofiltration [99]. Prophylactic hemodialysis immediately after the administration of LO-CM in 113 patients with a renal insufficiency (baseline creatinine > 204 μmol/L) did not diminish the rate of complications, including CN (*level I*) [100]. In contrast, periprocedural hemofiltration effectively prevented a decline in renal function and additionally improved in-hospital and one year survival (*level I)*. This was shown in a RCT in 114 consecutive patients with chronic renal insufficiency (creatinine > 177 μmol/L) undergoing coronary angiography and/or intervention with LO-CM [101]. Hemofiltration at a rate of 1000 ml/h started 4 to 6 hours before the procedure, was resumed after the procedure to be continued for 18 to 24 hours. Control patients received a continuous infusion of normal saline at a rate of 1 ml/kg/h for 6 to 8 hours, or 0.5 ml/kg/h if ejection fraction was less than 40 %, before and 24 hours after the procedure. The relative risk of death in the control group was not significantly different in the patients with baseline creatinine less than 355 μmol/L, but relative risk was 3.53 (95 % CI 1.08 to 11.20), if baseline creatinine concentration was 355 μmol/or higher, significantly higher than in the hemofiltration group. The beneficial effect on outcome may be explained by an interplay of several factors. First, the hemofiltrated patients received a higher level of care, intensive- versus high care. Secondly, hydration in patients with combined cardiac and renal insufficiency may be complicated by pulmonary oedema. Furthermore, the rather high volume of contrast in this study, about 250 ml, explained by the concomitant coronary intervention, might have temporarily aggravated both cardiac and renal dysfunction. Hemofiltration might have contributed to stabilisation of circulation and control of pulmonary edema. Finally, even a relatively low dose of hemofiltration doubles total body clearance of the radiocontrast if renal insufficiency is severe and this was the subgroup with benefit.

> *Prophylactic hemofiltration reduces in-hospital and cumulative one-year mortality in patients renal dysfunction undergoing cardiac catheterisation, specifically in the subgroup of patients with baseline creatinine greater than 4 mg/dl . Apply hemofiltration in patients with severe cardiac and renal dysfunction (grade B). Do not use prophylactic hemodialysis (Grade B).*

Conclusion

Contrast nephropathy is a common cause of iatrogenic acute renal failure. Its incidence rises with the growing use of intra-arterial radiocontrast in older patients for diagnostic and interventional procedures. Nephrotoxicity is related to osmolality, dose and route of the contrast agent and only occurs in synergy with other factors, such as previous renal impairment, cardiovascular disease and the use of certain drugs. Contrast nephropathy

has impact on morbidity and mortality. Several measures are of proven benefit in the prevention of contrast nephropathy in patients at risk. Among them are the use of low osmolal contrast, discontinuation of potentially nephrotoxic drugs, pre-hydration, especially with isotonic sodium-bicarbonate, N-acetylcysteine, theophylline and high dose ascorbic acid. In patients with severe cardiac and renal dysfunction undergoing cardiac interventions, periprocedural hemofiltration may be considered.

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Table 1. Mechanisms of contrast induced nephrotoxicity

- afferent vasoconstriction
- medullary ischemia
- direct cytotoxicity
- oxidative tissue damage
- apoptosis

Table 2. Risk factors for the development of contrast-induced nephropathy.

Patient related
- Pre-existing renal dysfunction, especially diabetic nephropathy
- Dehydration, vascular contraction
- Congestive heart failure
- Vascular disease
- Age over 70 years
- multiple myeloma

Concurrent medication related
- NSAID's, dipyridamol [68], acetaminphen,
- aminoglycosides
- amfotericine B
- cyclosporin
- chemotherapeutics, such as cisplatinum
- antiviral drugs, such as acyclovir and foscarnet

Contrast related
- use of high osmolal contrast
- use of a high contrast volume
- use of the intra-arterial route

Table 3. Randomised controlled trials comparing different hydration regimes in patients receiving intravascular high-osmolar (HO) or low-osmolar (LO) contrast medium (CM) for coronary angiography (CAG), angiography (angio) or CT scanning on the incidence of contrast nephropathy (CN) or glomerular filtration rate (GFR in ml/min). SCr: serum creatinine 1 mg/dl corresponds to 88.4 µmol/l. PA pulmonary artery, PAWP pulmonary artery wedge pressure.

Author reference	Nr pat	Inclusion SCr mean baseline Cr	Study intervention	Contrast type, route, volume	Incidence of CN	Level
Trivedi H [44] 2003 Nephron Clin Pract 93:C29	27-26	SCr 106 ± 28 µmol/l	NaCl 0.9 % 1 ml/kg/h from 12 h before vs. free oral intake	LO-CM CAG 201 - 187 ml	3.7 vs 35 % p = 0.005	II
Solomon R [44] 1994 New Engl J Med 331:1416	28-25-25	SCr > 141 µmol/l or clearance < 60 ml/min 186 - 186 - 186 µmol/l	NaCl 0.45 % 22h before and after vs idem + mannitol 25 g 60 min before vs idem + furosemide 80 mg 30 min before	HO-CM 32% LO-CM 67% CAG 130 ml	11 vs 28 vs 40 % p = 0.02 (vs sal)	II
Mueller C [7] 2002 Arch Int Med 162:329	685-698	all patients 81 - 82 µmol/l	Na Cl 0.9% i ml/kg/h from 8 AM to 8 AM vs NaCl 0.45 % Glucose 2.5 %	LO-CM 67% CAG 234 ml	0.7 vs 2.0 % p = 0.04	I
Stevens M [45] 2002 J Am Coll Cardiol 33:403	55 - 43	SCr > 159 µmol/l 230 vs 212 µmol/l	PA catheter in all, hydration from 1h before to 6h after iv NaCl 0.45% 150 ml/h vs iv NaCl 0.45% + furosemide+dopa+ mannitol if PAWP < 20 mm Hg	LO-CM 71% CAG 164 ml	18.2 vs. 11.6 % p = 0.37	I
Merten G [47] 2004 JAMA;291:2331	59-60	SCr > 97 µmol/l 150 - 168 µmol/l	154 mEq/l NaCl in dextrose 5% vs 154 mEq/l Nabic in dextrose 5% 3 ml/kg/h 1 h before, 1 ml/kg/h during and 6 h after	LO-CM CAG, CT, angio 132 ml	13.6 vs 1.7 % p = 0.02	I
Bader B [46] 2004 Clin Nephrol 62:1	20-19	normal 71 vs. 80 µmol/l	2000 ml from 12h before to12h after vs 300 ml NaCl 0.9% during contrast	LO-CM CT or angio 211 ml	5.3 vs. 15 % p = 0.6 ΔGFR 18.3 vs 34.6 p < 0.05	II

Table 4. Randomised controlled trials in patients receiving intravenous (i.v.) or intra-arterial (i.a.) high-osmolar (HO) or low-osmolar (LO) contrast medium (CM) on the effect of N-acetylcysteine (NAC) and theophylline (theo) or aminophylline (amino) on the incidence of contrast nephropathy (CN) or glomerular filtration rate (GFR). SCr: serum creatinine 1 mg/dl corresponds to 88.4 µmol/l. Level: level of evidence (see table I), ver: verum, plac: placebo, CAG coronary angiography, HD: hemodialysis.

Author reference	Nr pat ver-plac	Inclusion verum - plac. mean baseline SCr	Hydration	Study intervention	Contrast type, route, volume volume	Incidence of CN verum-plac	Level
				oral NAC vs. placebo			
Tepel M [48] 2000 NEJM 343:180	41-42	SCr > 106 µmol/l or clearance < 50 ml/min Cr 221 - 212 µmol/ll	iv NaCl 0.45 % 1 ml/kg/h	oral NAC 600 mg 2 dd vs. placebo day before & day of contrast	LO-CM i.v., CT scan 75 ml	reduced 2 vs. 21 %, p=0.01	II
Briguori C [20] 2002 J Am Coll Cardiol 40:298	92-91	SCr > 106 µmol/l or Cr.clear. < 70 ml/min Cr 133 - 133 µmol/l	iv NaCl 0.45 % 1 ml/kg/h	oral NAC 600 mg 2 dd vs. saline alone day before & day of contrast	LO-CM CAG, arterial 194 - 200 ml	not sign. Different 6.5 vs 11 %, p = 0.22 if < 140 ml was given: 0% vs. 8,5%, p = 0.02	I
Diaz-Sandoval L [22] 2002 Am J Cardiol 89:356	25-29	S Cr > 124 µmol/lor Cr clear. < 50 ml/min Cr 150 - 142 µmol/l	in NaCl 0.45% 1 ml/kg/h	oral NAC 600 mg 2 dd vs. placebo 1 dose before, 3 doses after	LO-CM elective CAG 179 - 189 ml	reduced 8 vs. 45 %, p = 0.005	II
Allaquabrand S [51] 2002 Cathet Cardiovasc Intervent 57:279	40-38-45	SCr > 142 µmol/l Cr 177 - 173 - 195 µmol/l	iv NaCl 0.45 % 1 ml/kg/h	oral NAC 600 mg 2dd vs. saline alone vs. fenoldopam 0.1 µg/kg/min	LO-CM CAG 122 - 129 - 122 ml	NAC 17.7 fenoldopam 17.7 % saline 15.3 %	II
Durham JD [52] 2002 Kidn Int 62:2202	38-40	SCr > 150 µmol/l Cr 195 - 204 µmol/l	iv NaCl 0.45 % 1 ml/kg/h	oral NAC 1200 mg 1-h before and 1200 mg 3-hours after vs placebo	LO-CM CAG 77 . 85 ml	not sign. different 26.3 vs 22.0 %	II
Shyu KG [49] 2002 J Am Coll Cardiol 40:1383	60-61	SCr 177-230 µmol/l clearance 8-40 ml/min Cr 248 - 248 µmol/l	iv NaCl 0.45% 1 ml/kg/h	oral NAC 400 mg 2 dd or placebo day before & day of contrast	LO-CM CAG 119 - 115 ml	reduced 3.3 vs 15 %, p < 0.001	I
Kay J [50] 2003 JAMA 289:553	102-98	SCr > 106 µmol/l no NT drugs Cr 115 - 106 (med) µmol/l	iv NaCl 0.9% 1 ml/kg/h	oral NAC 600 mg 2 dd vs. placebo day before & day of contrast	LO-CM CAG 120 - 130 ml	reduced 12 vs 4 %, p = 0.006	I
Oldemeyer JB [8] 2003 Am Heart J 16:E23	49-47	SCr > 106 µmol/l Cr clear. < 50 ml/min Cr 142 - 150 µmol/l	iv NaCl 0.45% 1 ml/kg/h	oral NAC 1500 mg 2 dd vs. placebo evening before 2dd 4 doses	LO-CM CAG 134 - 127	not sign. different 8.2 vs. 6.4%, p = 0.74	II
Goldenberg I [53] 2004 Eur Heart J 25:212	41-39	SCr > 133 µmol/l clearance < 50 ml/min 177 - 168 µmol/l	iv NaCl 0.45% 1 ml/kg/h	oral NAC 600 mg 2 dd vs. placebo from 12 h before to 12 h after	LO-CM CAG 116 ml	not sign. different 10 vs. 8 %, p = 0.47	II
Fung J [54] 2004 Am J Kidney Dis 43:801	46-45 open label	SCr 150-398 µmol/l Cr 204 - 212 µmol/l	iv NaCl 0.9% 100 ml/h	oral NAC 400 mg 3 dd day before & day of contrast vs. no drug	LO-CM CAG 136 - 121	not sign. different 17.4 vs. 13.3 %, p = 0.8	II
				iv NAC vs. placebo			
Baker CSR [55] 2003 J Am Coll Cardiol 41:2114	41-39	SCr > 120 µmol/l or Cr.clear. < 50 ml/min Cr 168 - 159 µmol/l	iv NaCl 0.9% 1 ml/kg/h	iv NAC 150 mg/kg in 500 ml 0.9% in 30 min pre, 50 mg/kg in 500 ml in 4 h post vs. placebo	LO-CM CAG 238 - 155	reduced incidenc with the higher dose 5 vs. 12.5 %, p = 0.045	II
				oral NAC single vs. double dose			
Briguori C [59] 2004 Eur Heart J 25:206	114: 1200 mg 110: 600 mg	SCr > 133 µmol/l Cr.clear. < 60 ml/min	iv NaCl 0.45% 1 ml/kg/h	oral NAC 600 mg 2 dd vs. oral NAC 1200 mg 2 dd	LO-CM CAG, peripheral AG	11% vs. 3.5 %, p = 0.038 no sign difference if contrast volume < 140 ml	I
				theophylline vs placebo			
Erley CM [63] 1994 Kidney Int 45:1425	19-20	> 100 ml LO-CM Cr 106 - 106 µmol/l	not mentioned	iv theo 5 mg/kg vs. placebo	LO-CM > 100 ml i.v. or i.a.	p: sign decrease in GFR theo: no decrease in GFR	II
Katholi RE [64] 1995 Radiology 195:17-22	24-24-22-23	SCr < 2.0 µmol/l Cr 115 - 106 µmol/l	oral or iv dextrose 1.43 ml/kg/h	oral theo 2.88 mg/kg 2 dd 4 times starting 1 h before vs. placebo LO-CM vs HO-CM	LO-CM or HO-CM CAG mean 111 ml	HO-CM GFR sign better in theo after 24 & 48h LO-CM GFR sign better in theo after 24h, not after 48h	II
Kolonko A [65] 1998 J Nephrol 11:151	26-32	SCr < 124 µmol/l Cr 89 - 89 µmol/l	not mentioned	theo 165 mg i.v. vs. placebo	HO-CM 40 ml aorta or iv	no decline vs. significant decrease in GFR	II
Abizaid S [36] 1999 Am J Cardiol 83:260	20-20-20	SCr > 133 µmol/l Cr 168 - 204 - 168 µmol/l	iv 0.45% NaCl 1 ml/kg/h	i.v. amino 4 mg/kg + 0.4 mg/kg/h vs. saline alone vs. dopamine 2.5 µg/kg/min	LO-CM mean 180-227-198 ml CAG	no difference 30%-35%-50%	II
Erley CM [69] 1999 Nephrol Dial Transplant 14:1146	35-29	SCr > 133 µmol/l > 100 ml LO-CM Cr 168 - 150 µmol/l	oral or iv NaCl 0.45% 2-2.5 L/d	oral theo 270 mg morning/ 540 mg evening, 2 d before & 3 d after vs. placebo	LO-CM mean 130-120 ml i.v. > i.a.	no difference 4.7 vs 3.4 %	II
Huber W [67] 2002 Radiology 223:772	50-50	SCr > 115 µmol/l > 100 ml LO-CM Cr 168 - 186 µmol/l	on clinical signs, >2 L/d was advised	iv theo 200 mg 30 min before vs. placebo	LO-CM > 100 ml i.a. (72%) i.v. (28%)	reduced 4 vs 16 %, p = 0.046	I
Kapoor A [66] 2002 Nephrol Dial Transplant 17:1936	35-35	DM Cr 106 - 106 µmol/l	i.v. NaCl 0.9% 1 ml/kg/h	oral theo 200 mg, 2 dd vs. hydration alone 1 day before & 2 d after	HO-CM CAG	reduced 3 vs. 31 %	II
Huber W 21] 2003 Am J Cardiol 91:1157	50-50	SCr > 115 µmol/l > 100 ml LO-CM Cr 150 - 150 µmol/l	> 2l/day was advised	iv theo 200 mg 30 min before vs. placebo	LO-CM CAG mean 197-217 ml	reduced 4 vs. 10%, p = 0.006	I
				iv theophylline vs. iv NAC			
Bader BD [70] 2002 (Abstract) J Am Soc Nephrol 13:2002	18-18	severe ren. insuff. vol. overload, card fail GFR 39 - 35 ml/min	not feasible	theo 5 mg/kg iv 30 min pre vs. NAC 600 mg iv pre and 600 mg iv 24h post CM	LO-CM > 60 ml LO-CM	theo: 28% no HD vs. NAC 39 %, 2 pat HD p = 0.045	II