

Contrast-induced nephropathy—prevention and risk reduction

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Abstract

Contrast-induced nephropathy (CIN) is a serious, but potentially preventable adverse event associated with the use of iodinated contrast media (CM). Studies suggest that the occurrence of CIN is directly related to the number of pre-existing patient risk factors such as pre-existing renal insufficiency (RI) with or without diabetes, advanced age, congestive heart failure and dehydration. Because the risk factors for CIN are common and the consequences serious or even life-threatening, it is important for physicians to implement preventive strategies. Although the optimal strategy for preventing CIN has not been fully established, it is important to first identify patients at risk. The commonly used methods for identifying patients at risk include use of patient questionnaires, review of medical history and measurement of serum creatinine levels prior to the administration of CM. Estimation of the glomerular filtration rate (GFR) before CM administration should be encouraged. To prevent the development of CIN, patients should be well-hydrated and nephrotoxic medications should be withdrawn at least 24 h prior to CM. Use of the minimal necessary CM dose is recommended, as the nephrotoxic effect of CM is dose-dependent. Furthermore, appropriate selection of CM is important. The incidence of CIN has been shown to be lower when an iso-osmolar CM rather than a low-osmolar CM (iohexol) is used in patients with RI and diabetes. Pharmacological intervention with calcium channel blockers, dopamine and N-acetylcysteine have not consistently been shown to reduce the incidence of CIN. This article will review the risk factors for the development of CIN and discuss practical strategies for its prevention in at-risk patients.

Keywords: contrast-induced nephropathy (CIN); iodixanol; iohexol; iso-osmolar; low-osmolar; osmolality; renal insufficiency

Introduction

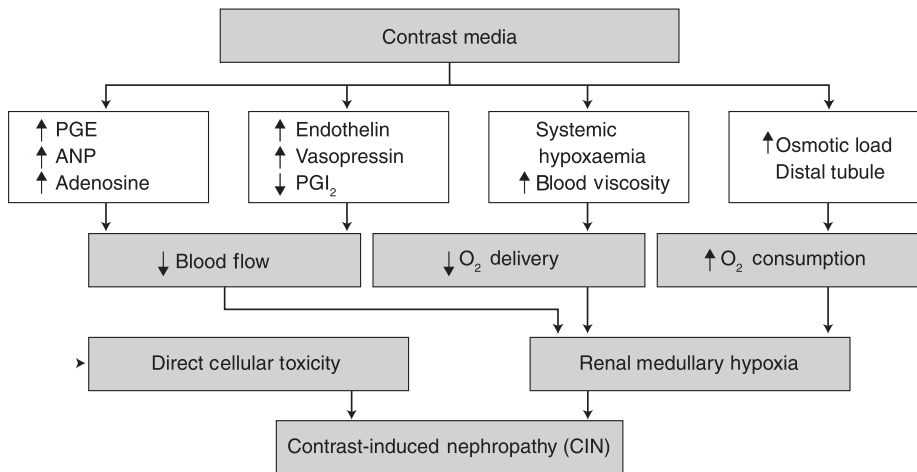
Contrast-induced nephropathy (CIN) is often a serious adverse event associated with the use of iodinated radiocontrast agents. The pathophysiology of CIN is complex and still not fully understood (Figure 1) [1]. It is thought that renal medullary hypoxia and direct tubular epithelial cell toxicity are the main factors responsible for CIN. Administration of contrast media (CM) causes intrarenal vasoconstriction mediated by a variety of factors including endothelin, vasopressin, calcium and adenosine, with subsequent reduction in blood flow leading to renal ischaemia that is most pronounced in the renal medulla, an area uniquely susceptible to ischaemic injury. This in turn appears to be compounded by the effects of reactive oxygen species produced by polymorphonuclear cells attracted to the site of tissue damage. Generation of these reactive oxygen species may also be mediated by calcium and adenosine, and by iodine in the CM.

The incidence of CIN reported in the literature varies markedly depending on the definition of CIN used, the type of procedure performed, the volume and type of contrast agent, patient risk factors—most notably the pre-existing renal insufficiency (RI) and diabetes—and the length of follow-up. McCullough [2] reported an overall incidence of 14.5% in patients undergoing coronary interventions. In patients without risk factors the incidence is ~2% [3], which appears low, but may amount to 600 000 cases per year in industrialized countries, in view of the large number of radiological examinations using iodinated CM. In patients with mild-to-moderate RI and diabetes, the incidence of CIN is reported in the range of 9 to >50% [4,5] and in patients with chronic diabetic azotaemic nephropathy, CIN can occur in 50–90% of the patients [6,7].

With advancing technology, the number of diagnostic and interventional procedures is growing and with it, the number of patients exposed to CM and at risk for CIN. The average number of whole body computed tomography scans, for example, has increased by 11% annually between 1995 and 2000 [8].

The number of patients with risk factors for CIN is also increasing. Retrospective and prospective studies

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ANP, atrial natriuretic peptide; PGE, prostaglandin; PGI, prostacyclin

Fig. 1. Pathophysiology of contrast-induced nephrotoxicity. Adapted with permission [1].

suggest that the occurrence of CIN is directly related to the number of pre-existing patient risk factors [9–11]. The prevalence of certain risk factors, such as advancing age and diabetes (and with it RI) is growing. Projections from the World Health Organization show that the population aged ≥ 60 years will increase from 600 million in 2000 to 1.2 billion in 2025 [12], and the worldwide prevalence of diabetes will increase from 171 million in 2000 to 366 million in 2030 [13].

There is no cure for CIN and treatment options are limited to supportive care. Because the risk factors for CIN are common and the consequences of this disorder can be serious, it is important for physicians using CM to incorporate preventive strategies into clinical practice [14].

While the optimal strategy for preventing CIN has not been fully established, physicians can take steps to reduce its occurrence. This article will review the risk factors for the development of CIN and provide practical strategies for preventing CIN in at-risk patients.

Identification of the patient at risk for CIN

Prevention of CIN begins with the identification of the patients who are most at risk. Commonly used methods to ascertain a patient's risk factors for CIN include use of patient questionnaires and a review of medical history [15,16]. An accurate assessment of kidney function is required and this is best achieved from measurement of serum creatinine (SCr) and estimation of the glomerular filtration rate (GFR) using either the Cockcroft–Gault or Modification of Diet in Renal Disease (MDRD) equations [17,18]. While nephrologists are familiar with these formulas, they should not assume that other medical specialties are similarly aware.

Independent risk factors for the development of CIN have been reported for patients undergoing cardiac catheterization, percutaneous coronary intervention (PCI) and coronary revascularization [2,4,5,10,11, 19–22]. Baseline demographic factors include: advanced age; clinical factors which include pre-existing high SCr, pre-existing renal impairment or chronic renal failure, low serum sodium level, low serum albumin, diabetes, hypertension, reduced left ventricular ejection fraction or congestive heart failure (CHF), previous coronary revascularization or bypass surgery, acute myocardial infarction (MI), shock, anaemia, peripheral vascular disease and prior stroke; and procedural factors include multivessel disease, hypotension, use of an intra-aortic balloon pump (IABP), CM type and volume of CM.

Risk assessment may be complicated by the presence of multiple risk factors. To simplify this process, Mehran *et al.* [10] developed a simple risk score for CIN after PCI for patients with >1 risk factor. Data were obtained from 8357 patients in a prospective interventional cardiology database who underwent PCI and had documented pre- and post-procedural SCr data. Patients requiring dialysis because of pre-existing end-stage renal disease (ESRD) were excluded from the analyses as were patients requiring more than one contrast procedure, those receiving PCI after acute MI and those in shock. Each patient was assigned to either a developmental dataset ($n=5571$) or a validation dataset ($n=2786$). The definition of CIN used in the analysis was an increase of $\geq 25\%$ or ≥ 0.5 mg/dl in baseline SCr at 48 h after PCI.

The mean age of patients in the developmental dataset was 63.8 years, and 28.8% of these patients were female. Mean baseline SCr was 1.12 mg/dl, and 10.5% of the patients had a baseline SCr >1.5 mg/dl indicating chronic kidney disease (CKD). Mean baseline estimated GFR (eGFR) was 72.7 ml/min/1.73 m² and 26.4% had an eGFR <60 ml/min/1.73 m²

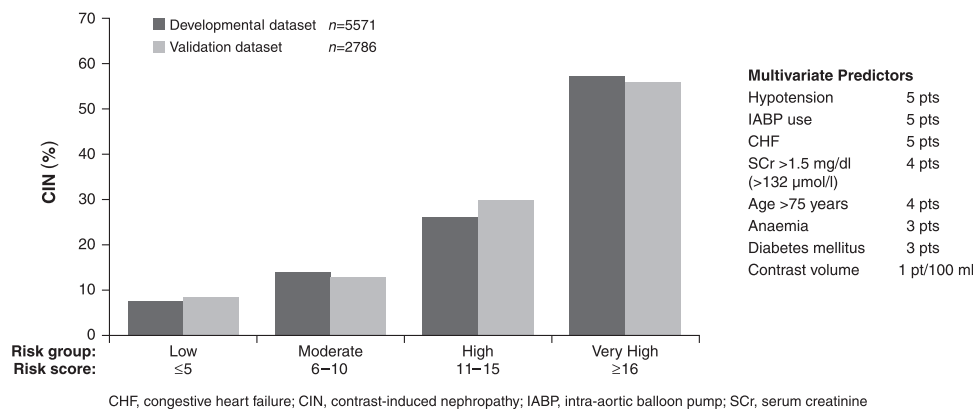


Fig. 2. Risk categories for the development of CIN in patients after undergoing PCI in developmental and validation datasets. The definition of CIN used in this study was an increase from baseline in SCr of $\geq 25\%$ or ≥ 0.5 mg/dl. Reprinted with permission [10].

indicating moderate renal impairment. Anaemia was present in 25.8% of the patients, diabetes in 30.7%, hypertension in 62.1%, hypercholesterolaemia in 69.8% and CHF in 6.0%. Multivessel disease was present in 26.9% of the patients, 15.8% received treatment to a saphenous vein graft lesion and 4% had treatment to a saphenous vein graft lesion and a native vessel lesion. An IABP was used in 7.1% of the patients (in approximately half of these patients as an emergency). The mean volume of CM was 260.9 ml, and 80.4% of the patients received >150 ml.

A total of 729 patients (13.1%) exhibited CIN. Candidate variables for conferring a significant risk for CIN were obtained using univariate analysis. The variables that were independently associated with CIN were then identified using multivariate analysis. Multivariate predictors were hypotension, IABP use, CHF, impaired renal function (SCr >1.5 mg/dl or >132 μ mol/l, age >75 years, anaemia, diabetes and increasing CM volume. Two multivariate models were used: one in which impaired renal function was defined according to SCr and the other in which it was based on eGFR. A risk stratification scoring system was developed using data from the two multivariate models with an integer score between one and six assigned to each variable (Figure 2).

Analysis of the incidence of CIN according to risk score demonstrated a significant trend for predicting CIN as the risk score increased ($P < 0.0001$). Using the frequencies of CIN in patients in the developmental dataset in relation to their risk scores, it was possible to categorize these patients into four groups according to the relative risk for CIN (Figure 2): low risk (scores ≤ 5), moderate risk (scores 6–10), high risk (scores 11–15) and very high risk (scores ≥ 16).

The predictive value of the risk score for CIN was assessed using data from the patients in the validation dataset. Out of these, 386 patients (13.9%) developed CIN after PCI. Patients in the validation and developmental datasets were assigned to risk categories based on their risk scores. The rates for CIN were similar for the validation and developmental datasets

within each risk category (Figure 2). In addition, the incidence of in-hospital dialysis (Figure 3A) and 1 year mortality (Figure 3B) were also shown to be greater for patients in the higher-risk categories compared with those in the lower-risk categories (Figure 3A and B). The development of this risk scoring system shows that individual patient risk for CIN and its associated complications following PCI can be estimated from a risk score calculated according to the patient's risk factors.

Nephrotoxic drugs

Exposure to nephrotoxic drugs should be restricted in at-risk patients undergoing contrast procedures. Agents that should be avoided for at least 24 h prior to administration of CM include non-steroidal anti-inflammatory drugs (both cyclo-oxygenase-1 and cyclo-oxygenase-2 inhibitors), aminoglycosides, ciclosporin, tacrolimus and amphotericin B [23,24].

Diuretics, angiotensin-converting enzyme inhibitors and statins

Furosemide and mannitol are diuretics that have been proposed as preventive agents for patients at risk for CIN because of their effects on renal blood flow. Furosemide inhibits electrolyte transport and attenuates medullary hypoxia. Mannitol is an osmotic diuretic with renal vasodilatory effects, although it is not known whether it increases blood flow to the renal medulla or to the cortex [25]. To date, clinical trial findings with these agents have been disappointing. The Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE) Study was a prospective, randomized, controlled trial of forced diuresis with furosemide and mannitol (the latter was given to patients with pulmonary capillary wedge pressure <20 mmHg) along with intravenous (IV) crystalloid, and low-dose dopamine vs IV

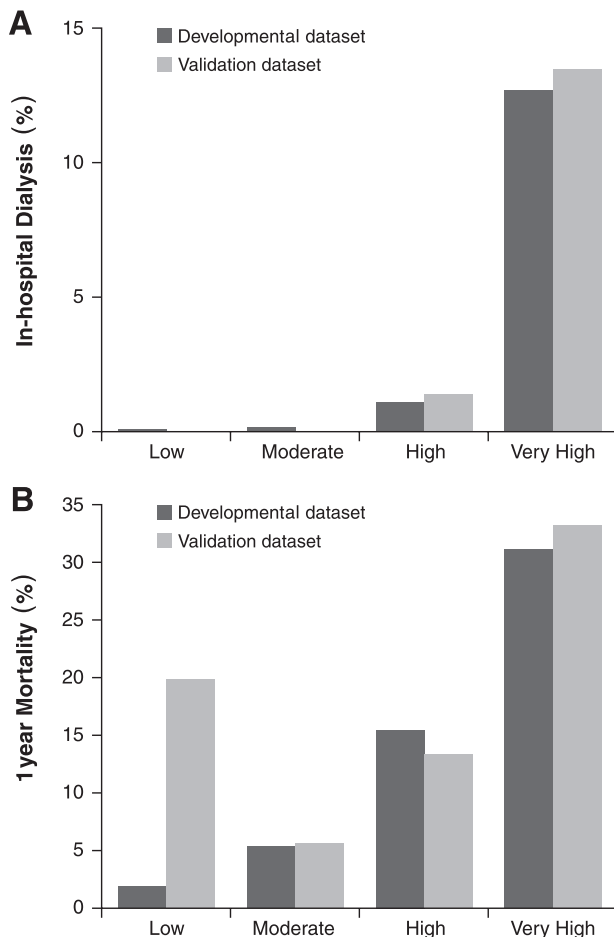


Fig. 3. Incidence of (A) in-hospital haemodialysis; and (B) 1 year mortality rate according to risk score for the development of CIN in developmental and validation datasets. Reprinted with permission [10].

crystalloid plus matching placebos in 98 patients with RI undergoing elective coronary angiography. Mean change in SCr at 48 h was not significantly different between the furosemide/mannitol/dopamine and control arms, and the rates of renal failure according to six different definitions were similar for both trial arms [26]. In two previous trials enrolling patients with RI undergoing coronary angiography or computed tomography, concurrent use of furosemide or furosemide/mannitol was associated with an increased incidence of CIN [27,28].

Because angiotensin-converting enzyme (ACE) inhibitors reduce renal perfusion, these agents have been thought to increase the risk for CIN. Limited data from a single randomized study of 71 diabetic patients undergoing coronary angiography showed that treatment with captopril, starting 1 h before contrast administration and continuing for 3 days afterwards, was associated with a 79% lower incidence of CIN (defined as a 0.5 mg/dl increase in SCr) [29]. More studies are needed to confirm a renoprotective effect of ACE inhibitors during CM administration.

Statins have been shown to have pleiotropic effects on the vasculature along with their efficacy for treating dyslipidaemia. The renoprotective effects of statins were investigated retrospectively in a study of 29 409 patients in whom baseline demographics and SCr were evaluated before and after PCI. Pre-procedural use of a statin was associated with a significantly lower incidence of CIN, defined as an increase in SCr of ≥ 0.5 mg/dl (4.37 vs 5.93%, $P < 0.0001$). These values correspond to an odds ratio (OR) for CIN of 0.87 [95% confidence intervals (CI), 0.77–0.99; $P = 0.03$] with statin use (after adjustment for comorbidities) [30]. Data from prospective, randomized studies are needed to confirm the efficacy of statins for preventing CIN.

Hydration

Hydration is a universally accepted component of protocols for preventing CIN [31–33]. The rationale for hydration is to prevent the renal vasoconstriction and subsequent hypoxia caused by contrast agents. The IV administration of saline before infusion of CM normalizes plasma volume; saline administration afterwards reduces osmotic diuresis [34].

Research into the optimal hydration protocol for preventing CIN has been limited by ethical considerations that preclude withholding any type of hydrating treatment and because controlled studies of hydration vs no hydration have not been possible owing to the lack of a placebo substitute for an IV infusion [32,33,35]. However, a few key studies have provided useful information on different hydration regimens for the prevention of CIN.

Trivedi *et al.* [36] prospectively compared the effects of IV hydration with normal saline with the provision of unrestricted oral fluids on the development of CIN in 53 patients who underwent non-emergency coronary angiography. Nearly all of the patients were male, 18.9% had diabetes, 43.4% had an acute MI and 34.0% received angioplasty and stent placement. The mean volume of CM used was 194.4 ml. The definition of CIN was a ≥ 0.5 mg/dl (≥ 44.2 μ mol/l) increase in SCr within 48 h of CM use.

A total of 10 patients developed CIN. IV hydration with normal saline was associated with a significantly lower incidence of CIN compared with unrestricted oral fluids (3.7 vs 34.6%; $P = 0.005$). These results support the use of IV hydration to reduce the risk of CIN in patients undergoing contrast procedures.

The type of fluid used for hydration has been investigated in two studies. The first was a prospective, randomized, controlled, open-label trial that compared the incidence of CIN in 1383 patients receiving normal (0.9%) or half-normal (0.45%) saline before elective or emergency coronary angioplasty [37]. Out of these patients, 74.4% were male, 20.7% had chronic renal disease and 15.7% had diabetes. Almost 60% of the coronary interventions were emergencies, and about 50% of the coronary lesions were complex.

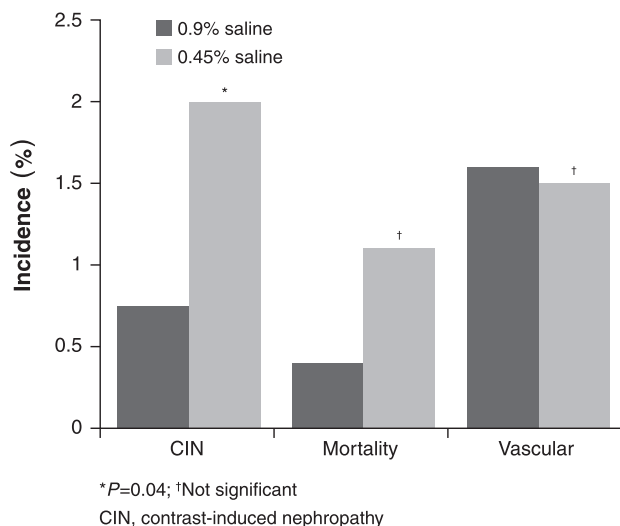


Fig. 4. The incidence of CIN, mortality and peripheral vascular complications among patients receiving normal and half-normal saline hydration in preparation for contrast procedures. Reprinted with permission [37].

The definition of CIN for the analysis was an increase in SCr ≥ 0.5 mg/dl (≥ 44 μ mol/l) within 48 h of CM administration.

A total of 19 patients developed CIN: five in the normal saline group and 14 in the half-normal saline group, corresponding to 0.7% (95% CI 0.1–1.4) and 2.0% (95% CI 1.0–3.1), of patients, respectively (Figure 4; $P=0.04$). The incidence of CIN was also analysed in three pre-defined subgroups: women, patients with diabetes and patients receiving ≥ 250 ml of CM. For all three subgroups, infusion with normal saline was associated with a significantly lower incidence of CIN compared with infusion of half-normal saline ($P=0.01$).

Analysis of cardiac complications was performed using data from 530 consecutive patients who had stent implantation. The incidence of major adverse cardiac events was not significantly different in the two study groups (Figure 4). The incidence of peripheral vascular complications was analysed in all the enrolled patients ($n=1620$). No significant difference was found in the incidence of peripheral vascular complications in the two study groups (Figure 4).

Because CIN is believed to involve production of reactive oxygen species, hydration that alkalinizes the urine may confer greater protection against CIN than hydration that merely expands plasma volume. In animal models of acute ischaemic renal failure, pre-treatment with sodium bicarbonate is more protective than saline. Merten and colleagues [38] compared isotonic sodium bicarbonate hydration ($n=60$) with saline hydration ($n=59$) for the prevention of CIN in patients with stable SCr of ≥ 1.1 mg/dl (≥ 97.2 μ mol/l). Out of these patients, 75% were male and 48% were patients with diabetes. More patients with severe RI (defined as SCr ≥ 221 μ mol/l) were randomized to the

sodium bicarbonate group than to the saline group (eight patients vs two). The definition of CIN in this study was an increase in SCr $\geq 25\%$ from baseline within 2 days of CM administration.

CIN occurred in one patient (1.7%) in the bicarbonate group compared with eight patients (13.6%) given saline ($P=0.02$). While these results are encouraging, this trial has a number of limitations: it was conducted in a single institution on a relatively small sample size, the investigators were not blinded and the statistical significance of the difference between the two groups depended on a single event. Confirmation of the potential of hydration with sodium bicarbonate is required in a large multicentre double-blind trial.

N-acetylcysteine

N-acetylcysteine (NAC) has a number of properties including anti-oxidant functions and mediation of renal vasodilation that suggest it could help prevent CIN [39]. Indeed, NAC is a part of the protocols to prevent CIN in many hospitals on the basis of the initial clinical study by Tepel *et al.* [40] and a number of subsequent clinical trials demonstrating renoprotective effects in patients receiving iodinated contrast agents. Other attributes of NAC that make it an attractive option include its ease of administration, good tolerability and low cost. However, NAC has been the subject of a comprehensive review, and overall there appears to be insufficient evidence to support the universal use of NAC to prevent CIN [39,41,42].

For example, the meta-analysis reported by Kshirsagar *et al.* [41] included 16 prospective, controlled trials that enrolled patients with RI (SCr ≥ 1.2 mg/dl or CrCl <70 ml/min/1.73 m²). Patients in the NAC groups were given the drug orally at a dose of 600 mg twice a day, 1 day before and on the day of exposure to CM in the majority of studies [41]. Findings for these trials were highly heterogeneous, such that it was not possible to estimate a meaningful summary effect of NAC on the risk for CIN (Figure 5). Meta-regression analysis identified several study and patient characteristics, with some evidence of association with study-specific estimates such as timing of NAC administration, volume and type of CM, advanced patient age and diabetes. It was not possible, however, to identify subsets of studies that were homogeneous enough to aggregate. The authors concluded that while study and patient characteristics may be the cause of some, but not all, of the heterogeneity, the results are too inconsistent to recommend the routine use of NAC for the prevention of CIN in patients with RI.

Finally, it should be noted that NAC may affect SCr levels independently of GFR. NAC appears to affect creatinine metabolism through activation of creatinine kinase [43], and in healthy volunteers who were given NAC, SCr levels were reduced but levels of cystatin-C were unchanged [44].

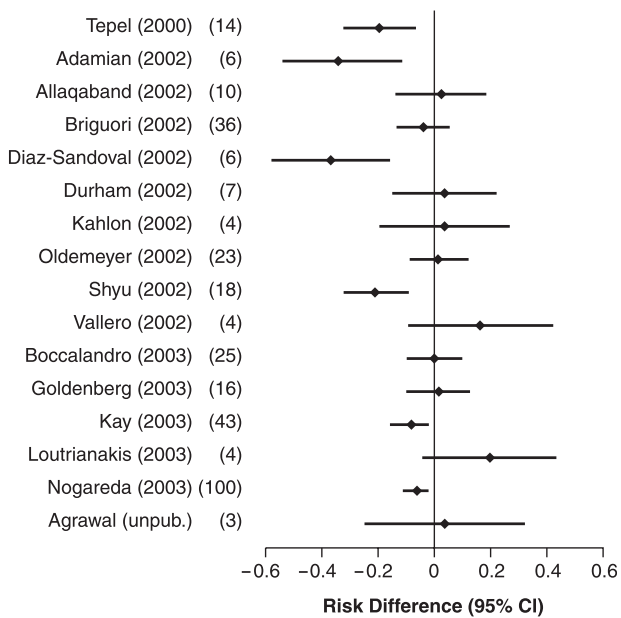


Fig. 5. Meta-analysis of studies of the prevention of CIN using NAC. Reprinted with permission [41].

Haemodialysis and haemofiltration

The rationale for haemodialysis in patients at high risk for CIN is to remove the CM from the patient's body as quickly as possible. Data on the efficacy of haemodialysis for preventing CIN is conflicting. A study reported by Moon *et al.* [45] in which 13 patients with RI and seven patients with end-stage renal failure underwent 6 h post-procedure haemodialysis found that 60–90% of the CM was removed and that none of the patients with RI demonstrated further deterioration of renal function. In a study of haemodialysis performed during coronary angiography in patients with advanced RI, no significant effects on renal function were observed in the patients who underwent haemodialysis compared with those who did not [46]. Finally, a study reported by Vogt *et al.* [47] found that haemodialysis performed after CM administration in patients with renal impairment was associated with a significantly greater mean peak in SCr ($P < 0.05$) compared with those who did not undergo haemodialysis. On the basis of these data, haemodialysis cannot be recommended because of the potential for deleterious effects on renal function.

Haemofiltration has also been proposed for rapid removal of CM in high-risk patients. The efficacy of haemofiltration for prevention of CIN was compared with isotonic saline hydration as a control procedure in a prospective randomized trial enrolling 114 patients with chronic renal failure (SCr > 2 mg/dl) who were undergoing coronary interventions [48]. The haemofiltration procedure was conducted in an intensive care unit, and both haemofiltration and hydration were started 4–8 h before the contrast procedure and were

continued for 18–24 h afterward. Mean SCr and blood urea nitrogen (BUN) were significantly lower for the haemofiltration group compared with the control group on days 1 through the discharge day (Figure 6). Mean urine output was significantly greater for the haemofiltration group compared with the control group on days 2 and 3. The incidence of CIN (defined as an increase in SCr $\geq 25\%$) was 5% in the haemofiltration group compared with 50% for the control group ($P < 0.001$). The rates for several other adverse outcomes were significantly lower for the haemofiltration group compared with the control group including in-hospital events (9 vs 52%, $P < 0.001$), in-hospital mortality (2 vs 14%, $P = 0.02$) and cumulative 1 year mortality (10 vs 30%, $P = 0.01$).

These findings on the effectiveness of haemofiltration for the prevention of CIN in patients with chronic renal failure are promising but require confirmation. The authors note that haemofiltration is a complex and costly procedure, but suggest that it may be considered for patients at a very high risk for CIN.

Contrast media

One method of classifying iodinated CM is on the basis of their osmolality. The high-osmolar CM (HOCM; e.g. diatrizoate, iohalamate, ioxithalamate) have an osmolality five to seven times greater than that of blood. These agents were developed in the 1950s and for many years were the mainstay of contrast-mediated procedures, but they are now rarely given by the intravascular route. Despite their rather misleading name, the low-osmolar CM (LOCM) introduced in the 1970s (e.g. iohexol, iopamidol, iopromide) are in fact hyperosmolar: two to three times greater than that of blood, and the newest class of contrast agent (e.g. iodixanol) is iso-osmolar to blood.

Within these three classes (high-, low- and iso-osmolar), it is possible to further subdivide CM in terms of their molecular structure (monomer vs dimer) and ionicity (ionic vs non-ionic) (Table 1) [49].

Nephrotoxicity of contrast media—clinical evidence

Although pre-clinical findings suggested that LOCMs would be less nephrotoxic than HOCMs, the clinical relevance of this was disputed for at least a decade. Several studies found no statistically or clinically significant differences in nephrotoxicity between HOCMs and LOCMs [4,27,50–53]. However, a meta-analysis reported by Barrett and Carlisle [54] demonstrated that LOCMs were associated with a significantly lower incidence of CIN than HOCMs ($P = 0.02$, using data from 5146 patients in 31 trials; results from 22 of the 31 trials in which these data were available favoured LOCMs). The OR for CIN (defined as a mean increase in SCr of $44 \mu\text{mol/l}$) with LOCMs was found to be 0.61 (95% CI 0.48–0.77; data were available for > 4000 patients in 25 trials) [54].

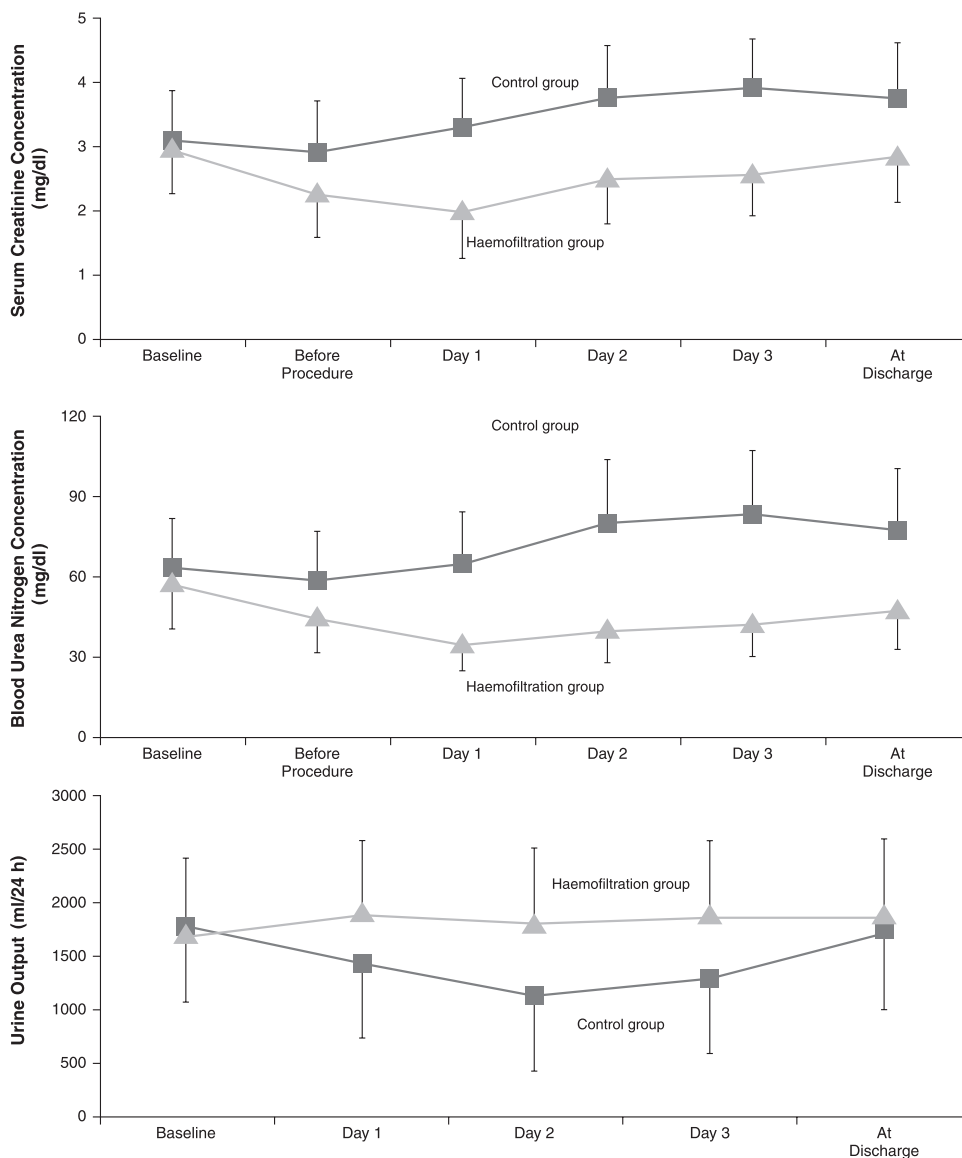


Fig. 6. Changes in SCr, BUN and urine output for the haemofiltration and the control (isotonic saline hydration) groups during a study of 114 consecutive patients with chronic renal failure undergoing coronary interventions. Significant differences between the two groups were noted for SCr and BUN on day 1 through the day of discharge and for urine output on days 2 and 3. Reprinted with permission [48].

Table 1. Physicochemical properties of contrast media. Adapted with permission [49]

Osmolality (mOsm/kg H ₂ O)	High-osmolar (2100)	Low-osmolar (577)	Low-osmolar (610–915)	Iso-osmolar (290)
Ionicity	Ionic	Ionic	Non-ionic	Non-ionic
No. of benzene rings	Monomer	Dimer	Monomer	Dimer
Viscosity at 37°C (cP)	8.4	9.5	7.8–11.2	11.1
Example	Diatrizoate	Ioxaglate	Iohexol Iopamidol Ioversol Iopromide	Iodixanol

Despite the statistical significance of these results, Barrett and Carlisle [54] qualify the interpretation of these findings. Given the number of patients included in these analyses and the trend among the studies

favouring LOCMs over HOCMs, the *P*-value of 0.02 for the incidence of CIN with LOCMs compared with HOCMs should not be interpreted as indicating a high level of significance. Furthermore, the pooled OR of

0.61 includes individual point estimates that lie at a distance from the pooled result despite the lack of significance observed in the test for heterogeneity ($P=0.48$).

Subgroup analyses by Barrett and Carlisle [54] were performed to determine if specific patient subgroups were responsible for the differences in the incidence of CIN observed in the meta-analysis. For patients with pre-existing renal failure, the OR for CIN with LOCMs was 0.5 (95% CI 0.36–0.7), whereas the OR for patients with normal renal function at baseline was 0.75 (95% CI 0.52–1.1). These findings indicate that it is the patients with pre-existing renal failure whose risk for CIN is reduced by using LOCMs instead of HOCMs. Patients with normal renal function have a similar risk for CIN with HOCMs and LOCMs. (It may be pointed out that there are other reasons to use LOCMs rather than HOCMs in patients with normal renal function such as the better cardiovascular safety profile and greater tolerability [55,56].)

The effects of several factors, including pre-existing renal failure and diabetes on the relative risk for CIN with the HOCM diatrizoate and the LOCM iohexol, were assessed in the large, prospective, randomized, double-blind, multicentre Iohexol Cooperative Study [57]. This trial enrolled 1196 patients, 364 of whom had normal renal function without diabetes mellitus (DM), 318 of whom had normal renal function and DM, 298 of whom had RI but not DM, and 216 who had RI and DM. The incidence of CIN (defined as an increase in SCr ≥ 1 mg/dl within 48–72 h after CM administration) was 3% in the iohexol group compared with 7% in the diatrizoate group ($P=0.002$). Multivariate analysis revealed the following independent risk factors for the development of CIN: RI (baseline SCr ≥ 1.5 mg/dl), DM, male sex and volume of contrast. For patients with pre-existing RI, the risk of CIN was 3.3 times greater (95% CI, 1.6–6.6) with diatrizoate than with iohexol. In patients with normal renal function, the risk of CIN was similar with iohexol and diatrizoate.

If contrast osmolality plays an important role in CIN and the evidence above shows LOCMs are less nephrotoxic than HOCMs in patients with risk factors such as RI and DM, the question arises whether an iso-osmolar contrast medium (IOCM) would in turn be associated with less CIN than a LOCM?

In a prospective, single-centre, randomized, unblinded trial, the incidence of CIN with the IOCM iodixanol and the LOCM iohexol, were compared in 124 patients with SCr >1.7 mg/dl (including 34 diabetic patients) undergoing renal and/or peripheral angiography [58]. The proportion of patients with an increase in SCr $>10\%$ was significantly lower for patients receiving iodixanol compared with that for patients receiving iohexol (15 vs 31%; $P < 0.05$).

The Nephrotoxicity in High-risk Patients (NEPHRIC) Study is the most definitive study to date, to compare the incidence of CIN in high-risk patients receiving IOCM and LOCM [59]. Conducted

in five European countries (Denmark, France, Germany, Spain and Sweden), this randomized, double-blind, prospective, multicentre study trial compared the renal effects of the IOCM iodixanol with those of the LOCM iohexol in 135 patients undergoing coronary or aortofemoral angiography who were at a high risk for CIN because of diabetes (type 1 and 2) and chronic renal failure (SCr 1.3–3.5 mg/dl for women and 1.5–3.5 mg/dl for men).

The study protocol recommended that all patients be well-hydrated according to the institutional regimens of the study centres before the start of angiography. The protocol recommended the following for all the study patients: 500 ml of water orally and/or 500 ml of saline IV followed by 1 l of 0.9% saline or similar fluids IV from the start of the procedure [59].

The primary endpoint was the peak increase in SCr between days 0 and 3 after CM administration. The secondary endpoints included the number of patients who developed CIN according to two definitions [an increase in SCr ≥ 0.5 mg/dl (44.2 $\mu\text{mol/l}$) on days 0 to 3 and a peak increase in SCr ≥ 1.0 mg/dl (88.4 $\mu\text{mol/l}$) on days 0 to 3] and the change in SCr from day 0 to 7.

The demographics and baseline clinical characteristics of the iodixanol and iohexol groups were not significantly different with the exception of mean body mass index (BMI; 26.8 vs 28.5 kg/m²) and the mean duration of diabetes (12.8 vs 18.0 years). The difference in BMI between the two groups was small. The difference in reported duration of diabetes between the two groups is unlikely to be relevant to the analysis of the study results. With type 2 DM, the actual duration of the disease is virtually impossible to determine exactly because a patient may be glucose intolerant for several years before it is detected clinically.

The mean peak increase in SCr on days 0 to 3 was significantly lower for patients receiving iodixanol [0.13 mg/dl (11.2 $\mu\text{mol/l}$)] compared with that for patients receiving iohexol [0.55 mg/dl (48.2 $\mu\text{mol/l}$; $P=0.001$)] (Figure 7A). Analysis of the mean peak increase in SCr between days 0 and 3 according to baseline SCr revealed another difference between the two treatment groups. A higher baseline SCr was associated with a greater mean peak SCr for patients receiving iohexol but not for patients receiving iodixanol (P for interaction <0.001).

The results of the secondary endpoints in the NEPHRIC study were also consistent with the greater nephrotoxicity of the LOCM (Figure 7B and C). A smaller proportion of patients in the iodixanol group developed CIN according to the two study definitions: SCr increased by ≥ 0.5 mg/dl in 3 and 26% of the iodixanol and iohexol groups, respectively ($P=0.002$), and by ≥ 1.0 mg/dl in 0 and 15% of the iodixanol and iohexol groups, respectively (Figure 7B). The odds of developing CIN using the definition of an increase in SCr ≥ 0.5 mg/dl was 11 times greater for the iohexol group than the iodixanol group. The mean change in SCr between days 0 and 7 was significantly lower for the iodixanol group [0.07 mg/dl (6.3 mmol/l)]

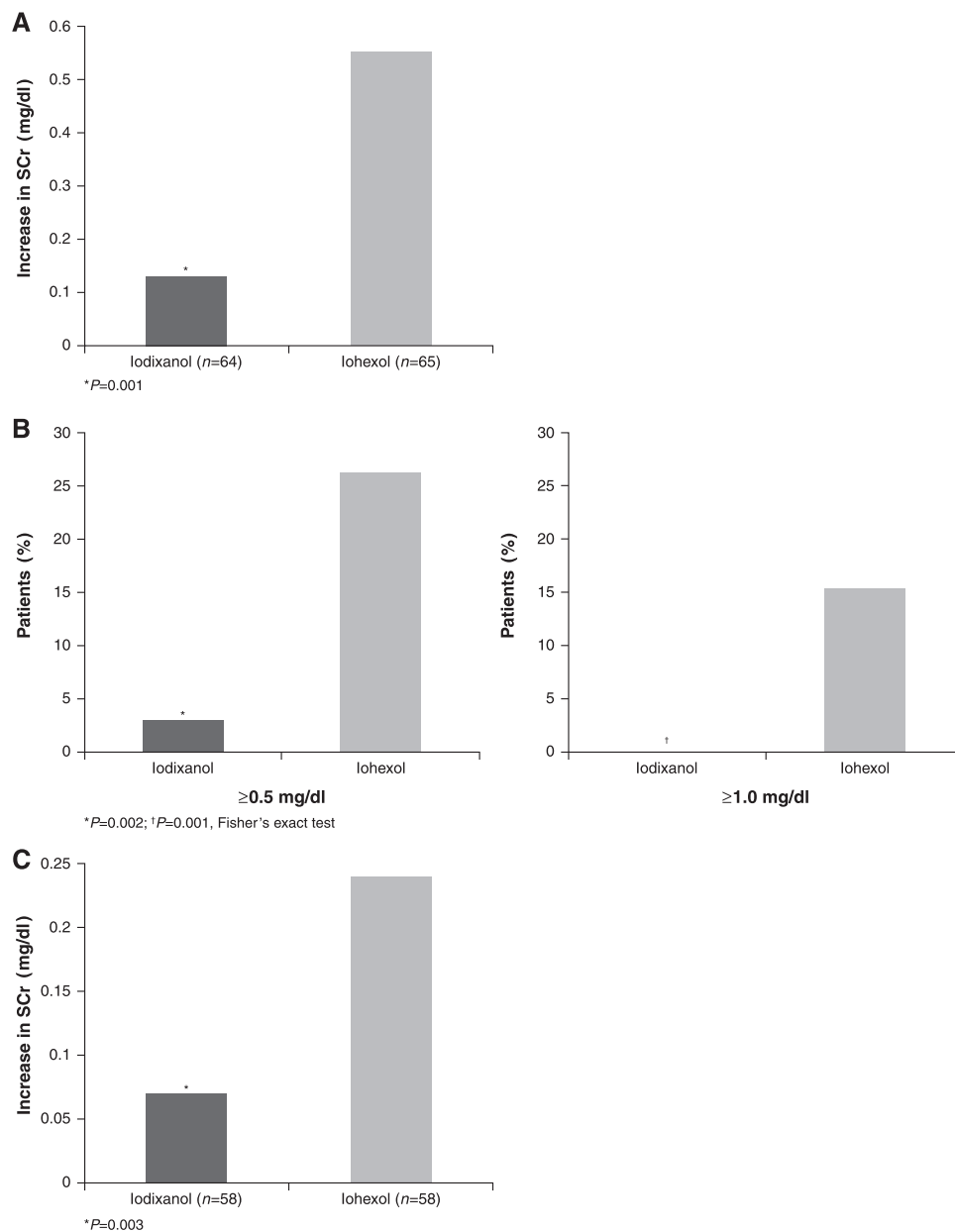


Fig. 7. Findings from the Nephrotoxicity in High-risk Patients (NEPHRIC) Study: (A) Mean peak increase in SCr between days 0 and 3 after CM administration (primary endpoint); (B) proportion of patients exhibiting a peak increase from baseline in SCr of ≥ 0.5 mg/dl and ≥ 1.0 mg/dl (secondary endpoint), reprinted with permission; (C) mean change in SCr up to day 7 after CM administration (secondary endpoint) [59].

compared with that for the iohexol group [0.24 mg/dl (21.4 mmol/l); $P = 0.003$; Figure 7C].

Seven serious adverse events were judged to be contrast-induced, all in the patients who received iohexol: five with acute renal failure and one with both acute renal failure and arrhythmia. Out of these six patients, three recovered, two died and one had persistent renal failure.

Contrast media—osmolality or viscosity?

The relative importance of osmolality and viscosity of CM in CIN is the subject of some debate. While some

experimental studies might suggest that the higher viscosity of dimeric CM could be problematic because, for example, it could limit the flow in renal tubules [60], there is no evidence from randomized prospective clinical trials to support the contention that contrast viscosity causes CIN. In fact, although the pathogenesis of CIN is still not completely understood, clinical evidence to date suggests that contrast osmolality plays a far more significant role in CIN [57–59], and as the osmolality of CM has steadily decreased with the introduction of new agents, from HO-CM to LO-CM, and most recently from LO-CM to IO-CM, the

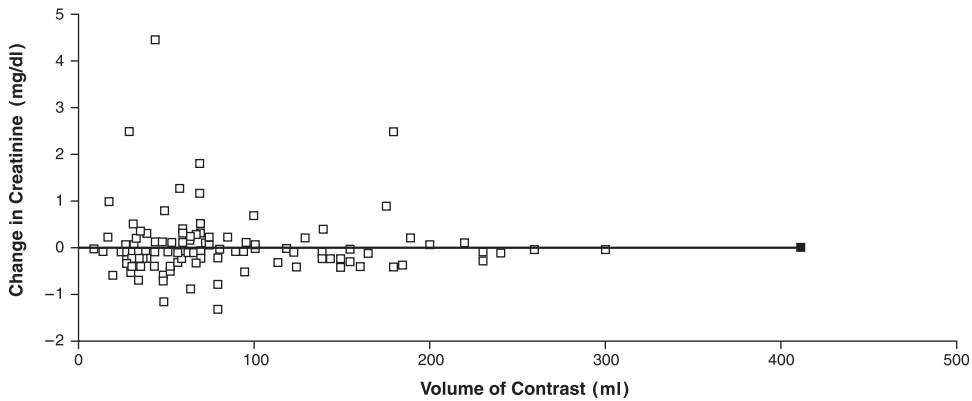


Fig. 8. Scatter-plot and linear regression analysis of change in SCr according to the volume of iodixanol received by 117 patients with RI (creatinine clearance [CrCl] rate <60 ml/min) undergoing cardiac catheterization. Reprinted with permission [64].

incidence of CIN in clinical studies has declined most notably in patients at risk.

Contrast media volume and nephrotoxicity

Studies by McCullough *et al.* [2] and Freeman *et al.* [61] in which patient enrolment was not restricted to those with RI, noted an association between CM volume and development of CIN. However, CM volume is an especially important issue for patients with RI. A retrospective study by Taliercio *et al.* [62] of 139 patients with renal impairment (SCr ≥ 2.0 mg/dl) undergoing coronary angiography found that administration of ≥ 125 ml CM was a significant risk factor for CIN (defined as increase in SCr > 1.0 mg/dl at any point between days 1 and 5) compared with the use of < 125 ml ($P = 0.05$), particularly in patients without additional risk factors. Similar results were observed for patients with RI by Gruberg *et al.* [22] and Briguori *et al.* [63]. Repeat procedures within 72 h have been associated with CIN in patients with renal impairment [14,62]. For patients with very low eGFR (< 30 ml/min), even small volumes of CM have been associated with an increased risk of CIN. A study by Manske *et al.* [6] of risk factors for CIN (defined as an increase in SCr $> 25\%$ at 48 h) in 59 azotaemic, insulin-dependent patients undergoing coronary angiography observed a 50% incidence of CIN. Independent risk factors for CIN by univariate analysis included ejection fraction $\leq 50\%$, low mean arterial pressure and CM volume ≥ 30 ml. The latter was associated with an OR of 10.6 (95% CI 2.08–60.6; $P = 0.002$), and linear regression revealed that every 5 ml increment of CM was associated with an OR for CIN of 1.44 (95% CI 1.07–1.94; $P = 0.03$).

The high-risk patients in the study by Manske *et al.* [6] received the LOCMs iohexol or iopamidol. A retrospective study by Tadros *et al.* [64] assessed the correlation between volume of iodixanol used and development of CIN in 117 patients with CKD (GFR < 60 ml/min) undergoing cardiac

catheterization. These patients received a mean of 84.3 ± 67.3 ml of iodixanol. The mean peak in SCr was 0.03 ± 0.07 mg/dl, and the incidence of CIN (SCr increase by > 0.5 mg/dl or $> 25\%$) was 18.8%. The mean volume of iodixanol received by patients who developed CIN was not significantly different from that received by patients who did not ($P = 0.922$). Linear regression revealed no significant correlation between the volume of iodixanol and the change in SCr ($r = 0.0011$; $P = 0.7254$) (Figure 8). Subanalysis of data from 18 patients with severe RI (eGFR < 30 ml/min) and 25 patients with severe RI and diabetes also showed no significant correlation between iodixanol volume and SCr change (data not shown).

An algorithm for management of patients undergoing contrast investigation

Although the optimal strategy for preventing CIN has not been fully established, several preventive measures are supported by clinical trial data. Figure 9 provides an algorithm adapted from Goldenberg and Matetzky [65], outlining the management of patients undergoing contrast procedures.

The first step is to estimate the patient's risk for CIN. The commonly used methods for identifying patients at risk include use of patient questionnaires, review of medical history and measurement of SCr levels prior to administration of CM. Calculation of the eGFR should be encouraged, and the more formal, yet simple scoring system developed by Mehran *et al.* [66] can provide a semi-quantitative estimate of the patient's risk.

For the high-risk patient, alternative diagnostic modalities should be considered. If, however, no viable alternatives exist, nephrotoxic medications should be withdrawn for at least 24 h and IV normal saline hydration should be provided before and after the procedure. The smallest volume of CM should be used. HOVM should be avoided; instead, a LOCM,

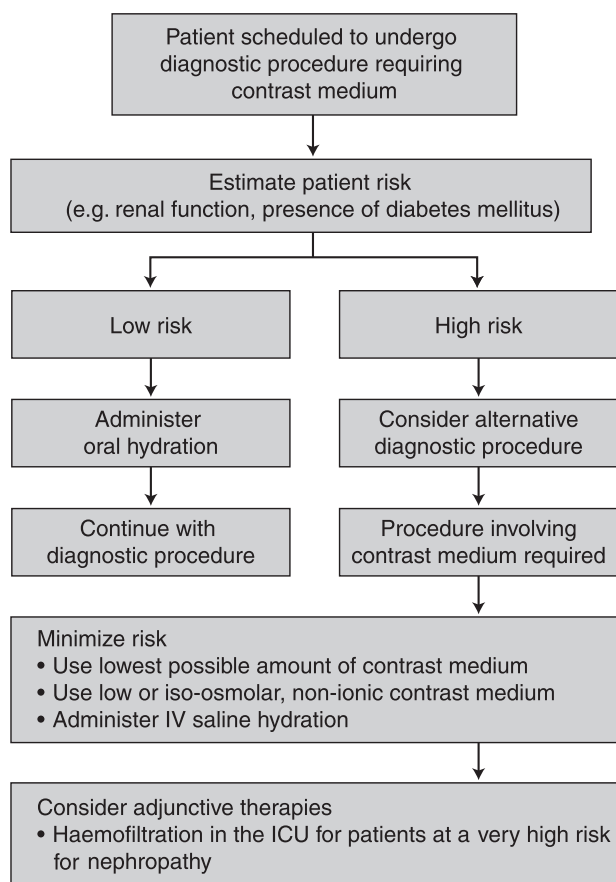


Fig. 9. An algorithm for management of patients undergoing contrast investigations. Adapted with permission [65].

or an IOCM should be administered. It has been shown in high-risk patients that an IOCM (iodixanol) results in lower rates of CIN than a LOCM (iohexol) [59]. The clinical trial data on NAC are equivocal, and its use is questionable, although it seems unlikely to do harm and is inexpensive. Haemofiltration, although expensive and supported by only limited data, may be considered for patients at a very high risk.

Conclusions

Because CIN is a potentially serious adverse event for which treatment options are limited to supportive care, physicians using CM should incorporate preventive strategies into their clinical practices. The consulting nephrologist can provide guidance to radiologists and cardiologists regarding the identification of patients at risk and practical strategies to reduce the incidence of CIN. These include assessment of patient risk, IV saline hydration and use of the lowest volume possible of the appropriate contrast agent.

Conflict of interest statement. See full declaration on *NDT* website: www.ndt.oxfordjournals.org.

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