Effectiveness of Prophylactic Strategies for Contrast-Induced Nephropathy

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Abstract

Introduction: Contrast-induced acute kidney injury, also referred to as contrast-induced nephropathy (CIN), is a potentially serious renal complication associated with the use of iodinated contrast media (CM) in patients at risk. With the dramatic growth in contrast-enhanced imaging services worldwide, including procedures involving exposure to iodinated CM, efforts to reduce the occurrence of CIN have received considerable attention in recent years. To date, these efforts have met with little success since the 12% prevalence of CIN today remains unchanged from 2 decades ago.

Methods: We conducted a systematic literature review of the most recent evidence available from published reports of contemporary (2000-2008) prospective, randomized, controlled trials that have investigated CIN either by comparing CM or by comparing preventive strategies. The objective was to critically review the findings in light of several aspects of study design and then to establish a set of parameters for consideration in the planning of future CIN trials so as to optimize the strength of evidence obtained.

Results: Whether future CIN trials are investigating comparative CM nephrotoxicity or dealing with prophylactic strategies for risk reduction, the complexities that must be addressed include a standardized definition of CIN, appropriate timing of SCr measurements with timing standardized for all subjects in a given study population, awareness of study population risk profile, hydration protocols, and pharmacological prophylactic strategies.

Conclusions: Large, well-designed trials (ideally with hard clinical outcome measures) that consider all the complexities involved in CIN and its prevention are needed before the clinical community has the evidence-based direction required for optimized patient care.

Key Words: Contrast-induced nephropathy; Iodinated contrast media; Pharmacologic prophylaxis; Randomized controlled trials

Introduction

Over the past decade there has been dramatic growth worldwide in contrast-enhanced imaging services, many involving exposure to iodinated contrast media (CM) (1, 2). While contrast-enhanced procedures are safe in the majority of cases, serious complications can occur in patients who are vulnerable. One of the potentially serious complications associated with iodinated CM use is contrast-induced nephropathy (CIN), a condition that is often transient but in some cases can lead to devastating clinical outcomes. Retrospective studies have demonstrated associations between CIN and prolonged hospitalization, higher rates of in-hospital clinical complications and increased in-hospital and 1-year mortality (3-7).

Contrast-induced nephropathy is most commonly defined as an absolute increase in baseline serum creatinine concentration (SCr) of at least 0.5 mg/dL (44.2 µmol/L) or a relative increase of 25% that occurs, in the absence of an alternate etiology, within 48 hours of contrast exposure (8, 9). The incidence of CIN is low, <5% in patients without risk factors, but is increased among patients with chronic kidney disease (CKD), particularly those who also have diabetes mellitus (8, 10, 11). Other reported CIN risk fac-
tors include advanced age, congestive heart failure, nephrotoxic drug use, hypovolemia and excessive CM volume, with metabolic syndrome, prediabetes and hyperuricemia among the more recently identified risk factors (8, 12, 13). The incidence of CIN may be as high as 50% in patients with multiple risk factors (7, 10).

The burden of CIN is likely to increase. The most important risk factor for CIN, CKD, affects 16.8% of the US adult population; this represents a 16% increase over prior data and is driven, in part, by the increasing prevalence of both diabetes mellitus and hypertension (14). In addition, the world population is aging, and more elderly patients are undergoing contrast-enhanced procedures (15, 16). Furthermore, recent concerns about nephrogenic systemic fibrosis associated with gadolinium-based magnetic resonance imaging agents may create a demand for procedures that use iodinated CM (17). Thus, the potential for an increase in the incidence of CIN in coming years is high. Strong evidence-based direction from well-designed clinical trials is therefore needed to optimize outcomes following contrast-enhanced procedures.

This systematic literature review will examine recent evidence from published reports of contemporary (2000-2008) prospective randomized controlled trials (RCTs) that have investigated CIN either by comparing CM or by comparing preventive strategies. Although CM safety has been the focus of many trials over the last few decades we were interested in focusing on issues investigated in trials of CM use in contemporary practice. The time frame selected coincides with the introduction of the iso-osmolar class of contrast agents in the late 1990s and the first trial – in 2000 – that compared the relative nephrotoxicity of the iso-osmolar CM (IOCM) ioxixanol with a low-osmolar CM (LOCM). Since 2000 – but not before – there has been intense activity in the area of clinical trials comparing the safety of iso-osmolar CM versus a variety of different LOCMs – as well as intense activity regarding novel strategies for CIN prevention other than through CM selection.

The objective of this systematic literature review is to critically examine the CIN trial findings in light of study design and to establish a set of parameters for consideration in the planning of future CIN trials so as to optimize the strength of evidence obtained.

**LITERATURE SEARCH: METHODS AND RESULTS**

Four different combinations of relevant terms were used to search Medline for potential articles: (i) contrast agent, hydration, sodium bicarbonate; (ii) contrast agent, nephrotoxicity, N-acetylcysteine (NAC); (iii) ioxixanol, iotrolan, nephropathy; and (iv) contrast agent, hemodialysis, nephropathy. The searches were restricted to the period January 2000 to April 2008 and to RCTs. Reference lists of selected articles and tables of contents from selected journal Web sites were reviewed for relevant publications not retrieved in the Medline searches. Because of the detailed information needed for this report, full-length publications were considered the most appropriate material. Abstract databases and meeting programs were not consulted.

From the 253 articles initially retrieved through these searches, 54 were selected for inclusion. Studies were eliminated if (i) they were not RCTs; (ii) the comparative interventions and/or outcomes described did not address the development or prevention of iodinated contrast-induced nephrotoxicity specifically; (iii) they were pilot studies or had a population ≤20; or (iv) findings were not clearly reported.

The prospective randomized trials selected represent studies that investigated (i) the comparative nephrotoxicity of IOCM versus LOCM contrast agents (6 trials) comparing iodixanol to a LOCM (18-23); (ii) the comparative benefit of different volume expansion strategies for CIN prevention (5 trials) (24-28); (iii) the comparative renoprotective effect of bicarbonate versus sodium chloride volume expansion for CIN prevention (5 trials) (29-33); (iv) the role of NAC in CIN prevention (27 trials) (29, 34-59); (v) the role of other pharmacologic agents in CIN prevention (10 trials) (24, 31, 55, 60-66); and (vi) the use of temporary renal replacement (hemofiltration or hemodialysis) in CIN prevention (5 trials) (37, 67-70). (Note: 5 of the 54 studies included more than 2 arms and therefore appear in more than 1 category (24, 29, 31, 37, 55).

Among the 54 studies selected, 8 were in the computed tomography (CT) setting (18, 21, 24, 25, 33, 34, 57, 70), and 1 involved a patient population that underwent noncoronary intra-arterial angiographic procedures (39). The majority of studies were in the interventional cardiology setting.

**Findings**

**Contrast agent**

Data from 6 RCTs that compared the relative nephrotoxicity of the IOCM iodixanol versus LOCM show considerable variability (Tab. I). Two trials, NEPHRIC (23) and RECOVER (22), found that iodixanol was associated with a significantly lower CIN incidence than the comparator LOCMs iohexol and ioxaglate, respectively. This benefit of IOCM was not observed in the most recently reported trial, however, which found a higher CIN incidence for iodixanol compared with iomeprol (18). In each of 3 other trials, no significant difference in CIN incidence was found between iodixanol and the comparator LOCMs iopamidol (19, 21) or iopromide...
<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication</th>
<th>Inclusion characteristics</th>
<th>N</th>
<th>Definition of CIN</th>
<th>Volume expansion</th>
<th>NAC use (patients, %)</th>
<th>Compara- tor LOCM</th>
<th>% CIN IOCM</th>
<th>% CIN LOCM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomsen et al 2008 (18)</td>
<td>Hepatic CE-MDCT</td>
<td>SCr ≥1.5 mg/dL and/or CrCl 10-59 mL/min per 1.73 m²</td>
<td>148</td>
<td>1SCr ≥0.5 mg/dL at 48-72 h</td>
<td>Center-specific decision and protocol; 12% of patients received ~1,200 mL, i.v.</td>
<td>Not used</td>
<td>iomeprol</td>
<td>6.9</td>
<td>0</td>
<td>0.025</td>
</tr>
<tr>
<td>Solomon et al 2007 (19)</td>
<td>Coronary angiography/PCI</td>
<td>GFR 20-59 mL/min per 1.73 m²</td>
<td>414</td>
<td>1SCr ≥0.5 mg/dL at 45-120 hours</td>
<td>Pre- and post-procedure volume expansion; isotonic NaHCO₃ i.v. 3 mL/kg per hour; 1 hour pre, 6 hour post</td>
<td>1,200 mg p.o./b.i.d; day -1 and +1; 38.7% (iodixanol); 42.4% (iopamidol)</td>
<td>lopamidol</td>
<td>6.7</td>
<td>4.4</td>
<td>0.39</td>
</tr>
<tr>
<td>Feldkamp et al 2006 (20)</td>
<td>Coronary angiography</td>
<td>Normal renal function (GFR ≥50 mL/min)(actual: 93.5 ± 22.0 mL/min)</td>
<td>221</td>
<td>1SCr ≥25% at 48 hours</td>
<td>Periprocedural volume expansion; 800 mL oral +1 L 0.9% NaCl i.v.; ~½ hour pre, until 10-12 hours post</td>
<td>Not used</td>
<td>lopamidom</td>
<td>8.6</td>
<td>6.9</td>
<td>0.83</td>
</tr>
<tr>
<td>Barrett et al 2006 (21)</td>
<td>Hepatic CE-MDCT or CE-MDCT of the peripheral arteries</td>
<td>SCr ≥1.5 mg/dL or CrCl &lt;60 mL/min</td>
<td>166</td>
<td>1SCr ≥0.5 mg/dL 48-72 ± 6 hours</td>
<td>Center-specific decision and protocol; 65% of patients received ~600 mL i.v. volume expansion</td>
<td>Not used</td>
<td>lopamidol</td>
<td>2.6</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Jo et al 2006 (22)</td>
<td>Coronary angiography/PCI</td>
<td>CrCl ≤60 mL/min</td>
<td>300</td>
<td>1SCr ≥0.5 mg/dL or ≥25% day 1-2</td>
<td>Pre- and post-procedure volume expansion; 0.45% NaCl, i.v. 1 mL/kg per hour, ≥8 hours</td>
<td>Not used</td>
<td>ioxaglate</td>
<td>7.9</td>
<td>17.0</td>
<td>0.021</td>
</tr>
<tr>
<td>Aspelin et al 2003 (23)</td>
<td>Coronary or aortofemoral angiography</td>
<td>Diabetes mellitus, SCr 1.5-3.5 mg/dL, CrCl ≤60 mL/min</td>
<td>129</td>
<td>1SCr ≥0.5 mg/dL day 0-3</td>
<td>Pre- and post-procedure volume expansion recommended; ~1 L i.v. fluid administered (0.9% saline, or similar)</td>
<td>NAC (protocol details NA) 6.3% (iodixanol); 10.8% (iohexol)</td>
<td>iohexol</td>
<td>3.0</td>
<td>26.0</td>
<td>0.002</td>
</tr>
</tbody>
</table>

b.i.d. = twice daily; CE-MDCT = contrast-enhanced multidetector computed tomography; CIN = contrast-induced nephropathy; CM = contrast medium; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; IOCM = iso-osmolar CM; i.v. = intravenous; LOCM = low-osmolar CM; NAC = N-acetylcysteine, PCI = percutaneous coronary intervention; p.o. = orally; SCr = serum creatinine.
TABLE II
INCIDENCE OF CIN IN RANDOMIZED CONTROLLED TRIALS COMPARING VOLUME EXPANSION STRATEGIES

<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication</th>
<th>Inclusion characteristics</th>
<th>N</th>
<th>Definition of CIN</th>
<th>CM</th>
<th>Volume expansion strategy</th>
<th>p  Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dussol et al 2006 (24)</td>
<td>Contrast-enhanced radiologic procedures,</td>
<td>CrCl 15-60 mL/min; CKD stage 3-4 (actual: mean CrCl 37 ± 12 mL/min; mean SCR 201 ± 81 µmol/L; 2.27 ± 0.92 mg/dL)</td>
<td>312*</td>
<td>↑SCR ≥0.5 mg/dL within 48 hours</td>
<td>Ioxaglate, iobitrindol, iopromide</td>
<td>Oral NaCl, 1 g/10 kg body weight per day, 2 days preprocedure</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td>including CT (predominantly) and coronary angiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NaCl i.v. (0.9%), 15 mL/kg, 6 hours preprocedure</td>
<td>5.2</td>
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<tr>
<td></td>
<td>(24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Bader et al 2004 (25)</td>
<td>Angiography/CT</td>
<td>Normal renal function (SCR 53-106 µmol/L; 0.60-1.20 mg/dL)</td>
<td>39</td>
<td>↓&gt;50% GFR in 48 h</td>
<td>Iopromide,ioxhexol</td>
<td>Bolus (300 mL saline) ≥2,000 mL i.v. NaCl 12 hours before and after CM administration</td>
<td>15.0</td>
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<tr>
<td></td>
<td>(25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.3</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.605†</td>
</tr>
<tr>
<td>Krasuski et al 2003 (26)</td>
<td>Cardiac catheterization</td>
<td>SCR 1.6-3.0 mg/dL</td>
<td>37</td>
<td>↑SCR ≥0.5 mg/dL within 48 hours</td>
<td>NA</td>
<td>Bolus (250 mL normal saline)</td>
<td>10.8</td>
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<tr>
<td></td>
<td>(26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
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<td></td>
<td></td>
<td>0.136</td>
</tr>
<tr>
<td>Trivedi et al 2003 (27)</td>
<td>Nonemergency coronary angiography</td>
<td>CrCl ≥20 mL/min (actual: mean CrCl, 79.6 ± 31.9 mL/min; mean SCR 1.20 ± 0.32 mg/mL)</td>
<td>53</td>
<td>↑SCR ≥0.5 mg/mL in 48 hours</td>
<td>Ionic LOCM</td>
<td>Unrestricted oral fluids</td>
<td>34.6</td>
</tr>
<tr>
<td></td>
<td>(27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.7</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Mueller et al 2002 (28)</td>
<td>Coronary angioplasty</td>
<td>None (end-stage renal failure excluded); mean CrCl, 84 ± 2 mL/min; mean SCR 0.92 ± 0.02 mg/dL</td>
<td>1,620</td>
<td>↑SCR &gt;0.5 mg/dL in 48 hours</td>
<td>Iopromide, iomeprol</td>
<td>Half-isotonic (0.45% NaCl + 5% glucose) i.v. before and after CM administration (24 hours total)</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>(28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

CIN = contrast-induced nephropathy; CKD = chronic kidney disease; CM = contrast medium; CrCl = creatinine clearance; CT = computed tomography; GFR = glomerular filtration rate; i.v. = intravenous; LOCM = low-osmolar CM; NA = not available; NaCl = saline; NS = not significant; SCR = serum creatinine. *n=76 in oral NaCl arm (A) and n=77 in i.v. NaCl arm (B); third arm (C), n= 80, and fourth arm (D), n=79, in this study compared the effect of addition of theophylline and furosemide, to IV NaCl, respectively (see Tab. V). †Significant benefit of i.v. preprocedural volume expansion over bolus in terms of mean decrease in GFR (p<0.05) but not in terms of CIN defined here as a 50% decrease in GFR at 48 hours.
Among these 6 RCTs, CIN incidences were low in 4, ranging from 0 to 8.6% (18-21), whereas in the RECOVER and NEPHRIC trials, high incidences, 17% and 26%, were observed for the respective LOCM arms (22, 23).

Preventive strategies

Volume expansion

Five selected trials investigated the timing and mode of saline volume expansion for CIN prevention (Tab. II). A strategy that includes both preprocedural and postprocedural intravenous (i.v.) 0.9% saline rather than half-strength saline appears to be superior to unrestricted oral fluids (27, 28), but whether or not it provides a benefit compared with an i.v. saline bolus during the procedure is unclear (25). Of note are the low CIN incidences, ≤5%, obtained for the i.v. saline route in all of the studies, whether or not volume expansion was continued postprocedure. A trial comparing preprocedural i.v. saline with combined preprocedure and postprocedure i.v. saline would be of interest, given the potential practical value of a simplified prophylactic strategy for use, for example, in high-volume diagnostic CT clinical settings.

In the 5 trials that compared bicarbonate with saline volume expansion, bicarbonate was consistently associated with a significantly lower rate of CIN; however, considerable variation in CIN incidence was observed across studies (Tab. III) (29-33).

### TABLE III
INCIDENCE OF CIN IN RANDOMIZED CONTROLLED TRIALS COMPARING BICARBONATE VERSUS SALINE VOLUME EXPANSION

<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication</th>
<th>Inclusion characteristics</th>
<th>N</th>
<th>Definition of CIN</th>
<th>CM</th>
<th>% CIN NaHCO₃</th>
<th>% CIN NaCl</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozcan et al 2007</td>
<td>Coronary angiography/PCI</td>
<td>SCR &gt;1.2 mg/dL</td>
<td>264</td>
<td>↑SCR &gt;0.5 mg/dL or &gt;25% after 48 hours</td>
<td></td>
<td>4.5</td>
<td>13.6</td>
<td>0.036</td>
</tr>
<tr>
<td>Recio-Mayoral et al 2007</td>
<td>Emergency PCI for acute coronary syndrome</td>
<td>None</td>
<td>111</td>
<td>↑SCR ≥0.5 mg/dL in 3 days</td>
<td></td>
<td>1.8</td>
<td>21.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Briguori et al 2007</td>
<td>Coronary/peripheral angiography/angioplasty</td>
<td>SCR ≥2.0 mg/dL or eGFR &lt;40 mL/min per 1.73 m²</td>
<td>326</td>
<td>↑SCR ≥25% after 48 hours</td>
<td></td>
<td>1.9</td>
<td>9.9</td>
<td>0.019</td>
</tr>
<tr>
<td>Masuda et al 2007</td>
<td>Emergency diagnostic/interventional coronary procedures</td>
<td>SCR ≥1.1 mg/dL or eGFR &lt;60 mL/min</td>
<td>59</td>
<td>↑SCR &gt;0.5 mg/dL or &gt;25% within 48 hours</td>
<td></td>
<td>6.7</td>
<td>34.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Merten et al 2004</td>
<td>Diagnostic/interventional procedures requiring CM (including CT)</td>
<td>SCR ≥1.1 mg/dL</td>
<td>119</td>
<td>↑SCR ≥25% in 48 hours</td>
<td></td>
<td>1.7</td>
<td>13.6</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CIN = contrast-induced nephropathy; CM = contrast medium; CT = computed tomography; eGFR = estimated glomerular filtration rate; NAC = N-acetylcysteine; NS = not significant; PCI = percutaneous coronary intervention; SCR = serum creatinine.

*n=88 in NaHCO₃ arm and n=88 in NaCl arm; n=88 patients receiving saline + NAC in third arm (see Tab. IV).

†All patients received NAC, 111 with NaCl and 108 with NaHCO₃; n=107 patients receiving NAC with NaCl + ascorbic acid in third arm; % CIN = 10.3, NS in comparison with NAC + saline arm (Tab. V).
<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication</th>
<th>Inclusion characteristics</th>
<th>N</th>
<th>Definition of CIN</th>
<th>CM</th>
<th>% CIN +NAC</th>
<th>% CIN -NAC</th>
<th>P Value</th>
</tr>
</thead>
</table>
| Poletti et al 2007 (34) | Emergency contrast-enhanced CT procedures | Renal insufficiency (SCr >1.2 mg/dL or 106 µmol/L)               | 87   | ↑SCr ≥25% at 48 hours  
↑cystatin C ≥25% at 48 hours | Iopromide  
NAC i.v.; 900 mg × 2 | 5.0        | 21.0        | 0.026   |
| Seyon et al 2007 (35)  | Coronary angiography/PCI            | Acute coronary syndrome and renal insufficiency  
1.3 mg/dL; 1.4 mg/dL or 115 µmol/L; 125 µmol/L  
or CrCl <50 mL/min | 40   | ↑SCr >0.5 mg/dL or  
>25% within 48 hours | Iohexol, Iodixanol  
NAC oral; 600 mg × 4 | 2.5        | 5.0         | ---     |
| Carbonell et al 2007 (36) | Coronary angiography                | Acute coronary syndrome with normal renal function  
<1.4 mg/dL or 123.76 µmol/L | 216  | ↑SCr ≥0.5 mg/dL or  
>25% at 48 hours | Iopromide  
NAC i.v.; 600 mg × 4 | 10.3       | 10.1        | 0.5     |
| Ozcan et al 2007 (29)  | Coronary angiography/PCI            | SCr >1.2 mg/dL                                                  | 264t | ↑SCr >0.5 mg/dL or  
25% at 48 hours | Ioxaglate  
NAC oral; 600 mg b.i.d. × 2 days | 12.5       | 13.6        | 0.059   |
| Coyle et al 2006 (38)  | Coronary angiography                | Diabetes mellitus                                               | 137  | ↑SCr >0.5 mg/dL                  | NA                          | 9.2        | 1.4        | 0.043t  |
| Sandhu et al 2006(39)  | Noncoronary diagnostic angiography  | None (acute renal failure or renal transplant excluded)         | 106  | ↑SCr >0.5 mg/dL at 48 hours       | Iodixanol, Iopamidol      | 5.7        | 0          | ---     |
| Reinecke et al 2007 (37) | Elective coronary angiography       | SCr ≥1.3 mg/dL to ≤3.5 mg/dL                                   | 412l | ↑SCr ≥0.5 mg/dL from 48-72 hours   | Iopromide  
NAC oral; 600 mg × 4 | 5.3        | 6.1         | ---     |
| Marenzi et al 2006 (40) | Primary coronary angioplasty        | Presentation within 12 hours of MI symptom onset  
(actual renal function, normal: population median SCr 1.04 mg/dL; mean CrCl 78 ± 29 mL/min) | 354l | ↑SCr ≥25% within 72 hours         | Iohexol  
standard-dose NAC i.v.  
600 mg bolus + 600 mg oral b.i.d. × 2  
(3,000 mg, total)  
high-dose NAC 1,200 mg, as above (6,000 mg, total) | 15.0       | 33.0        | <0.001 |
| Kotlyar et al 2005 (58) | Coronary/peripheral angiography     | SCr ≥0.13 mmol/L                                                | 60   | ↑SCr ≥0.044 mmol/L within 48 hours    | Iopromide  
NAC i.v.;  
(group 1) 300 mg × 2  
(group 2) 600 mg × 2 | 0.04        | 0.0         | ---     |

CONTINUES
<table>
<thead>
<tr>
<th>Study</th>
<th>Procedure</th>
<th>Renal Function</th>
<th>CRF (mg/dL) or CrCl (mL/min)</th>
<th>CRF (mg/dL) or CrCl (mL/min)</th>
<th>CRF (mg/dL) or CrCl (mL/min)</th>
<th>iopamidol</th>
<th>NAC</th>
<th>Outcome</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Briguori et al 2004</td>
<td>Elective coronary/peripheral angiography/angioplasty</td>
<td>Chronic renal insufficiency (Scr ≥ 1.5 mg/dL and/or CrCl &lt; 60 mL/min)</td>
<td>224</td>
<td>&lt;0.5 mg/dL or &gt;25% at 48 hours</td>
<td>≥0.5 mg/dL at 48 hours or need for dialysis</td>
<td>11.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ochoa et al 2004</td>
<td>Coronary angiography/PCI</td>
<td>Documented renal insufficiency (Scr 1.8 mg/dL; 1.6 mg/dL or CrCl &lt; 50 mL/min)</td>
<td>80</td>
<td>&gt;0.5 mg/dL or &gt;25% at 48 hours</td>
<td>≥0.5 mg/dL or &gt;25% at 48 hours</td>
<td>8.3</td>
<td>25.0</td>
<td>0.051</td>
<td></td>
</tr>
<tr>
<td>Rashid et al 2004</td>
<td>Angiography/angioplasty for peripheral arterial disease</td>
<td>Normal renal function (Scr &lt; 1.32 mg/dL; 1.07 mg/dL or &lt; 120 μmol/L; 97 μmol/L)</td>
<td>94</td>
<td>≥0.5 mg/dL at 48 hours</td>
<td>≥0.5 mg/dL at 48 hours</td>
<td>0 (0/29)</td>
<td>0</td>
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<tr>
<td>Fung et al 2004</td>
<td>Elective coronary angiography/intervention</td>
<td>Moderate to severe renal insufficiency (Scr 1.69-4.52 mg/dL or 149-400 μmol/L)</td>
<td>91</td>
<td>≥0.5 mg/dL (or ↓ eGFR ≥25% within 48 hours)</td>
<td>≥0.5 mg/dL (or ↓ eGFR ≥25% within 48 hours)</td>
<td>17.4</td>
<td>14.3</td>
<td>0.8</td>
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<tr>
<td>Goldenberg et al 2004</td>
<td>Coronary angiography/PCI</td>
<td>Chronic renal insufficiency (Scr ≥ 1.5 mg/dL or CrCl &lt; 50 mL/min) Chronic renal failure (Scr &gt; 1.2 mg/dL or CrCl &lt; 50 mL/min)</td>
<td>80</td>
<td>≥0.5 mg/dL at 48 hours</td>
<td>≥0.5 mg/dL at 48 hours</td>
<td>10.0</td>
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<td>Boccalandro et al 2003</td>
<td>Cardiac catheterization</td>
<td>Elective cardiac catheterization with &gt; 1 mL/kg of contrast agent</td>
<td>179</td>
<td>≥0.5 mg/dL at 48 hours</td>
<td>≥0.5 mg/dL at 48 hours</td>
<td>13.0</td>
<td>12.0</td>
<td>0.84</td>
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<tr>
<td>Kefer et al 2003</td>
<td>Coronary angiography/PCI</td>
<td>Normal or mild-moderate renal function (Scr ≤ 3 mg/dL)</td>
<td>108</td>
<td>≥0.5 mg/dL or ≥25% at 24 hours</td>
<td>≥0.5 mg/dL or ≥25% at 24 hours</td>
<td>3.8</td>
<td>5.9</td>
<td>0.98</td>
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<td>El Mahmoud et al 2003</td>
<td>Coronary angiography/PCI</td>
<td>Chronic renal insufficiency (Scr &gt; 1.36 mg/dL or CrCl &lt; 50 mL/min)</td>
<td>120</td>
<td>≥25% at 48 hours or dialysis</td>
<td>≥25% at 48 hours or dialysis</td>
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<td>3.3</td>
<td>NS</td>
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<tr>
<td>Baker et al 2003</td>
<td>Coronary angiography/PCI</td>
<td>SCR &gt; 1.36 mg/dL or CrCl &lt; 50 mL/min</td>
<td>80</td>
<td>≥25% at 2 or 4 days</td>
<td>≥25% at 2 or 4 days</td>
<td>4.9</td>
<td>20.5</td>
<td>0.045</td>
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<td>Kay et al 2003</td>
<td>Coronary angiography</td>
<td>CrCl &lt; 60 mL/min</td>
<td>200</td>
<td>≥25% within 48 hours</td>
<td>≥25% within 48 hours</td>
<td>3.9</td>
<td>12.2</td>
<td>0.03</td>
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<tr>
<td>Oldemeyer et al 2003</td>
<td>Coronary angiography</td>
<td>CrCl &lt; 50 mL/min and SCr &gt; 1.2 mg/dL</td>
<td>8.2</td>
<td>≥0.5 mg/dL or ≥25% within 48 hours</td>
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<td>8.2</td>
<td>6.4</td>
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<tr>
<th>Study</th>
<th>Procedure</th>
<th>SCr or CrCl Criteria</th>
<th>Incidence</th>
<th>Treatment</th>
<th>Comparison</th>
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<tr>
<td>Durham et al 2002 (51)</td>
<td>Coronary angiography</td>
<td>SCr &gt;1.7 mg/dL</td>
<td>79</td>
<td>Iohexol</td>
<td>26.3 22.0 NS</td>
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<tr>
<td>Shyu et al 2002 (52)</td>
<td>Coronary angiography</td>
<td>SCr 2.0-6.0 mg/dL or CrCl &lt;40 mL/min</td>
<td>121</td>
<td>Iopamidol</td>
<td>3.3 24.6 &lt;0.001</td>
</tr>
<tr>
<td>Vallero et al 2002 (53)</td>
<td>Coronary angiography/transluminal angioplasty</td>
<td>Normal renal function subgroup</td>
<td>80</td>
<td>Iodixanol</td>
<td>5.7 8.8 NS</td>
</tr>
<tr>
<td>Vallero et al 2002 (53)</td>
<td>Coronary angiography/transluminal angioplasty</td>
<td>Mild renal insufficiency subgroup (SCr &gt;1.2 mg/dL)</td>
<td>20</td>
<td>NAC oral; 600 mg b.i.d. × 2 days</td>
<td>16.6 0 NS</td>
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<tr>
<td>Briguori et al 2002 (54)</td>
<td>Coronary/peripheral angiography/angioplasty</td>
<td>SCr &gt;1.2 mg/dL or CrCl &lt;70 mL/min</td>
<td>183</td>
<td>Iopromide</td>
<td>6.5 11.0 0.22</td>
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<tr>
<td>Allaqaband et al 2002 (55)</td>
<td>Cardiovascular procedures</td>
<td>SCr ≥1.6 mg/dL or CrCl &lt;60 mL/min</td>
<td>123††</td>
<td>Ioversol, iodixanol NAC oral; 600 mg b.i.d. × 2 days</td>
<td>17.7 15.3 ---</td>
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<tr>
<td>Diaz-Sandoval et al 2002 (56)</td>
<td>Elective cardiac catheterization</td>
<td>Stable chronic renal insufficiency (SCr ≥1.4 mg/dL or CrCl ≤50 mL/min)</td>
<td>54</td>
<td>Loxian</td>
<td>8.0 45.0 0.005</td>
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<tr>
<td>Tepel et al 2000 (57)</td>
<td>Elective CT procedures (primarily for evaluation of abdominal or thoracic illness)</td>
<td>Chronic renal insufficiency (SCr &gt;1.2 mg/dL or CrCl &lt;50 mL/min)</td>
<td>83</td>
<td>NAC oral; 600 mg b.i.d. × 2 days</td>
<td>2.0†† 21.0 0.01</td>
</tr>
</tbody>
</table>

b.i.d. = twice daily; CIN = contrast-induced nephropathy; CM = contrast medium; CrCl = creatinine clearance; CT = computed tomography; MI = myocardial infarction; NA = not available; NAC = N-acetylcysteine, NS = not significant; PCI = percutaneous coronary intervention; SCr = serum creatinine; t.i.d. = three times a day.

*Study underpowered, increasing the possibility of a Type II error.
†n=88 in saline arm and n=88 in NAC arm; n=88 patients given NaHCO₃ volume expansion in third arm (see Tab. III).
‡Note significant difference in favor of -NAC.
§Intravenous volume expansion was not used, because peripheral angiographic procedures are often performed as emergency or day cases.
¶352 evaluable (354 enrolled); n=119 received volume expansion alone (control), n=115 received standard-dose NAC treatment, and n=118 received high-dose NAC treatment.
#Combined data for 2 different NAC doses (300 mg, n=20; 600 mg, n=21).
**Comparison between standard- and high-dose NAC; no control group with volume expansion alone in this study.
††n=45 in NAC arm and 40 in saline arm; n=38 patients given saline plus fenoldopam (CIN=15.7%, NS) in third arm (see Tab. V); p=0.919 for comparison of CIN incidences 15.3% (saline), 17.7% (NAC), and 15.7% (fenoldopam).
‡‡75 mL contrast agent containing iodine 300 mg/mL.
§§Mean serum urea nitrogen decreased significantly in the NAC group from 51 ± 28 mg/dL at baseline to 44 ± 29 mg/dL at 48h (p<0.001); respective values in the control group were 44 ± 26 mg/dL and 47 ± 29 mg/dL (p=0.38).
Pharmacologic prophylaxis

The value of NAC for CIN prevention has been the focus of many studies (Tab. IV). Among the 27 identified here, all but 1 (39) report the use of prophylactic volume expansion as part of the protocol. The majority of trials compared NAC with no NAC: 6 demonstrated a significant benefit (40, 49, 50, 52, 56, 57), 1 showed a borderline benefit in favor of NAC (42) and 1 found a significant disadvantage in NAC use (38); 15 failed to detect a difference in CIN incidence between treatment arms, and no statistical comparison was reported in 1 trial (39).

With regard to other interventions (Tab. V), fenoldopam, an arterial vasodilator expected to increase renal blood flow, showed no benefit compared with placebo (62) or NAC (55, 60, 61). It is also not clear whether furosemide (63) theophylline (24, 63), ascorbic acid (31, 65) or the statin simvastatin (66) provide any advantage (Tab. V); in one study, endothelin receptor antagonism exacerbated CIN (64).

Temporary renal replacement

Evidence from 2 studies of extracorporeal filtration for CIN prevention indicate a significant benefit relative to volume expansion alone (67, 68) (Tab. VI). The extent to which the decreases in SCr levels reflect a true renoprotective effect of hemofiltration and not just a clearance effect remains to be clarified, however. Of the 3 studies that investigated the use of prophylactic hemodialysis, 2 found a significant renoprotective effect for immediate postprocedure dialysis compared with volume expansion alone (37, 69), whereas the third study found no difference in CIN but the possibility of harm with active treatment (70) (Tab. VI).

Potential sources for the confusion in CIN trial findings

General study design and study reporting

Several reviews have assessed published trials of CIN prophylaxis and found considerable variation in quality assessment issues, such as blinding and whether analysis was to be by intention-to-treat. Sample size estimates have also come under scrutiny and particularly estimates that may have been based on exaggerated effect sizes (71, 72). Examples of underpowered and poorly reported studies with no sample size statement can also be found in the latest CIN trial literature retrieved here (29, 35).

Definition of CIN

A number of different CIN definitions are represented among the 54 selected studies, potentially limiting comparisons. A 7.5-fold variation in CIN incidence can be found for a given study population depending on which of 4 recognized definitions is applied (73) (Fig. 1). To illustrate here, when defined as an increase in SCr ≥25% and as a decrease in creatinine clearance (CrCl) ≥20%, both at 48 hours after CM administration, the incidence of CIN was 8.6% with ioxidan and 6.9% with iopromide using the first definition but 19.7% and 22.2%, respectively, using the second (20) (Tab. I).

Serum creatinine measurement

There is currently a lack of standardization of SCr measurement across laboratories, limiting the accuracy and comparability of data (75). Several different assay methods are used for SCr determinations and laboratories differ in calibration methods employed (75). Where reference to assay methods are specified in the trials, the alkaline picrate method appears to be the most commonly employed, although enzymatic SCr determination is also noted (37). Given the likelihood of interlaboratory variations in SCr findings, use of a central laboratory is essential in multicenter trials where SCr is an outcome measure: for example, as specified in the 26-center study of fenoldopam prophylaxis (62).

The timing and frequency of postprocedural SCr measurement is an important source of variation in CIN trial findings, one directly related to interindividual differences in the effect of CM on kidney function. The challenge of accurately capturing the occurrence of CIN is illustrated by data from an older study that monitored SCr concentrations at baseline, 24 and 48 hours postprocedure and showed that if SCr had
<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication</th>
<th>Inclusion characteristics</th>
<th>N</th>
<th>Definition of CIN</th>
<th>CM</th>
<th>% CIN</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng et al 2006 (60)</td>
<td>Cardiac catheterization</td>
<td>SCR &gt;1.2 mg/dL</td>
<td>95</td>
<td>↑SCR &gt;0.5 mg/dL or &gt;25% on day 1, 2 or 3</td>
<td>iodixanol or nonionic LOCM (unspecified)</td>
<td>20.0</td>
<td>11.4</td>
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<tr>
<td>Briguori et al 2004 (61)</td>
<td>Coronary/peripheral angiography/angioplasty</td>
<td>SCR ≥1.5 mg/dL or CrCl &lt;60 mL/min</td>
<td>192</td>
<td>↑SCR ≥0.5 mg/dL at 48 hours</td>
<td>iodixanol</td>
<td>13.7</td>
<td>4.1</td>
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<tr>
<td>Allaqaband et al 2002 (55)</td>
<td>Cardiovascular procedures (coronary/peripheral)</td>
<td>SCR ≥1.6 mg/dL or CrCl ≤60 mL/min</td>
<td>123*</td>
<td>↑SCR &gt;0.5 mg/dL at 48 hours</td>
<td>ioversol, iodixanol</td>
<td>15.7</td>
<td>17.7</td>
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<tr>
<td>Stone et al 2003 (62)</td>
<td>Invasive cardiovascular procedures</td>
<td>CrCl &lt;60 mL/min</td>
<td>315</td>
<td>↑SCR ≥25% within 96 hours</td>
<td>Nonionic LOCM (unspecified), iodixanol</td>
<td>33.6</td>
<td>30.1</td>
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<tr>
<td>Dussol et al 2006 (24)</td>
<td>Contrast-enhanced radiologic procedures, including CT (predominantly) and coronary angiography</td>
<td>CrCl 15-60 mL/min (CKD stage 3-4); actual: mean CrCl 37 ± 12 mL/min; mean SCR 201 ± 81 µmol/L; 2.27±0.92 mg/dL</td>
<td>312*</td>
<td>↑SCR &gt;0.5 mg/dL within 48 hours</td>
<td>ioxaglate, iobitridol, iopromide theophylline: 5 mg/kg per os (before)</td>
<td>7.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Huber et al 2003 (63)</td>
<td>Coronary angiography</td>
<td>SCR ≥1.3 mg/dL (actual: mean SCR 1.71 ± 0.58 mg/dL)</td>
<td>100</td>
<td>↑SCR ≥0.5 mg/dL within 48 hours</td>
<td>lomeprol theophylline: 200 mg i.v. (before)</td>
<td>4.0</td>
<td>20.0</td>
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<tr>
<td>Dussol et al 2006 (24)</td>
<td>Contrast-enhanced radiologic procedures, including CT (predominantly) and coronary angiography</td>
<td>CrCl 15-60 mL/min (CKD stage 3-4); actual: mean CrCl 37 ± 12 mL/min; mean SCR 201 ± 81 µmol/L; 2.27±0.92 mg/dL</td>
<td>312*</td>
<td>↑SCR &gt;0.5 mg/dL within 48 hours</td>
<td>ioxaglate, iobitridol, iopromide furosemide 3 mg/kg i.v. (after)</td>
<td>15.2</td>
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CONTINUES
### TABLE V - CONTINUED

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<tr>
<th>Study</th>
<th>Procedure</th>
<th>Chronic renal insufficiency</th>
<th>LOCM</th>
<th>LOCM (unspecified)</th>
<th>p value</th>
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<td>Wang et al 2000 (64)</td>
<td>Cardiac angiography</td>
<td>Chronic renal insufficiency (SCr ≥2.0 mg/dL or 176.8 µmol/L)</td>
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<td>↑ SCr ≥0.5 mg/dL or ≥25% within 48 hours</td>
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<td>placebo</td>
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<td>Boscheri et al 2007 (65)</td>
<td>Coronary angiography or angioplasty</td>
<td>SCr &gt;1.4 mg/dL or &gt;120 µmol/L (actual: mean SCr 1.74 ± 0.4 mg/dL)</td>
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<td>↑ SCr ≥25% at 48 hours</td>
<td>Iodixanol</td>
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<td>-AA</td>
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<td>Briguori et al 2007 (31)</td>
<td>Coronary/peripheral angiography/angioplasty</td>
<td>SCr ≥2.0 mg/dL or eGFR &lt;40 mL/min per 1.73 m² (actual: median SCr 1.94 mg/dL; CrCl 34 ± 9 mL/min per 1.73 m²)</td>
<td>326</td>
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<td>↑ SCr ≥25% after 48 hours</td>
<td>Iodixanol</td>
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<tr>
<td>Jo et al 2008 (66)</td>
<td>Coronary catheterization and/or coronary intervention</td>
<td>CrCl ≤ 60 mL/min or SCr ≥1.1 mg/dL (actual: mean CrCl 54.43 ± 16.2 mL/min; SCr 1.26 ± 0.38 mg/dL)</td>
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<td>236</td>
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<tr>
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<td></td>
<td>↑ SCr ≥25% and/or ≥0.5 mg/dL within 48 hours</td>
<td>Iodixanol simvastatin, 160 mg total, in 40-mg doses (before and after)</td>
<td>2.5</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.4</td>
<td>1.00</td>
</tr>
</tbody>
</table>

AA = ascorbic acid; CIN = contrast-induced nephropathy; CKD = chronic kidney disease; CM = contrast medium; CrCl = creatinine clearance; CT = computed tomography; E = endothelin; f = furosemide; F = fenoldopam; i.v. = intravenous; LOCM = low-osmolar CM; NAC = N-acetylcysteine; NS = not significant; S = simvastatin; SCr = serum creatinine; T = theophylline

* n=38 in fenoldopam arm, 45 in NAC arm; n=40 patients given saline alone in third arm (see Tab. IV); p=0.919 for comparison of CIN incidences 15.3% (saline), 17.7% (NAC), and 17.7% (fenoldopam).

† n=77 in control arm (B) (i.v. NaCl alone), n=80 in theophylline arm (C), and n=79 in furosemide arm (D); n=76 in first arm (A) of this study, and evaluated the effect of oral NaCl volume expansion compared with i.v. NaCl (see Tab. II).

‡ n=107 patients received NAC with 0.9% NaCl + ascorbic acid. All patients in this study received NAC, 111 with 0.9% NaCl and 108 with NaHCO₃, in the 2 other study arms (Tab. III) in addition to the one here.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication</th>
<th>Inclusion characteristics</th>
<th>N</th>
<th>Definition of CIN</th>
<th>CM</th>
<th>% CIN</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Marenzi et al 2006 (67)</td>
<td>Invasive cardiovascular procedure</td>
<td>CrCl ≤30 mL/min</td>
<td>92</td>
<td>↑SCr &gt;25%*</td>
<td>Iopentol</td>
<td>25.8 (HF after)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.2 (HF before and after)</td>
<td>0.0013</td>
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<tr>
<td>Marenzi et al 2003 (68)</td>
<td>Coronary angiography/angioplasty</td>
<td>Chronic renal failure (Scr &gt;2 mg/dL and CrCl &lt;50 mL/min)</td>
<td>114</td>
<td>↑SCr &gt;25%*</td>
<td>Iopentol</td>
<td>5.1 (HF before and after)</td>
<td>&lt;0.001</td>
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<tr>
<td>Lee et al 2007 (69)</td>
<td>Coronary angiography/PCI</td>
<td>Stable ‘advanced’ renal failure (Scr &gt;3.5 mg/dL)</td>
<td>82</td>
<td>↑SCr &gt;1.0 mg/dL at discharge†</td>
<td>Iohexol</td>
<td>5.0 (HD after)</td>
<td>&lt;0.001</td>
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<tr>
<td>Reinecke et al 2007 (37)</td>
<td>Elective coronary angiography</td>
<td>Scr ≥1.3 mg/dL to ≤3.5 mg/dL</td>
<td>412²</td>
<td>↑SCr ≥0.5 mg/dL from 48-72 hours</td>
<td>Iopromide</td>
<td>15.9 (HD after)</td>
<td>0.008</td>
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<tr>
<td>Vogt et al 2001 (70)</td>
<td>Contrast-enhanced procedures, including CT</td>
<td>Chronic stable renal failure (Scr &gt;2.3 mg/dL or &gt;200 µmol/L)</td>
<td>113</td>
<td>↑SCr &gt;0.5 mg/dL or &gt;25% at any time point to day 6</td>
<td>LOCM (unspecified)</td>
<td>31.0 (HD after)</td>
<td>0.67</td>
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</tbody>
</table>

CIN = contrast-induced nephropathy; CM = contrast medium; CrCl = creatinine clearance; CT = computed tomography; HD = hemodialysis; HF = hemofiltration; LOCM = low-osmolar CM; NS = not significant; PCI = percutaneous coronary intervention; Scr = serum creatinine.

*No time point included in definition but Scr determined at day 1, 2 and 3 postprocedure.
†Mean length of stay was 13 ± 18 days for control group (volume expansion only) and 6 ± 3 days for HD group.
‡Of 424 enrolled patients, 412 were evaluable; n=113 in volume expansion+hemodialysis group and n=115 in control group (volume expansion alone); n=114, received volume expansion +NAC in third group (see Tab. IV).
been measured only at 24 hours, 58% of CIN cases would have been missed, while 18% would have been missed if SCr had been measured only at 48 hours (76) (Fig. 2).

With very few exceptions (18, 19, 21, 47) (Tabs. I and IV), the 54 studies identified here assessed SCr at baseline and at either a single, fixed, 48-hour time point or at multiple, fixed, time points from 1 to 3 or more days postprocedure. Among the trials that evaluated the relative nephrotoxicity of iodixanol versus LOCM, the 2 that compared iodixanol with iopamidol and the 1 that compared iodixanol with iomeprol each assessed CIN based on a single, random SCr determination rather than a standardized time point; in 1 trial, SCr was measured between 45 and 120 hours postprocedure (19) and in the other 2, between 48 and 72 hours (18, 21) (± 6 hours, mean 57.1 hours, in one of these) (21). Given these considerations and their impact on end point measures, the failure to detect a difference in comparative nephrotoxicity between iodixanol and iopamidol, and the apparent renal benefit of iomeprol relative to iodixanol await confirmation (Tab. I).

**Study population risk profile**

The majority of CIN trials in this review selected their study population using renal impairment as an inclusion characteristic. However, the different thresholds that were used to define impaired kidney function across trials may have led to heterogeneity in the degree of CIN risk among patient populations, explaining some of the variability in findings.

For example, among the NAC trials, representative threshold SCr levels used as the basis for renal insufficiency and study inclusion varied from >1.2 mg/dL (34) to >1.3 mg/dL in females and >1.4 mg/dL in males (35), to >1.5 mg/dL (41) (Tab. IV). The use of estimated glomerular filtration rate (GFR) in some trials (19, 20) and calculated CrCl in others (18, 21-23) (Tab. I) to define inclusion criteria for renal impairment may also introduce disparities across study populations, because renal impairment identified according to parameters...
in the Modification of Diet in Renal Disease (MDRD) study formula may not be comparable to that identified according to parameters in the Cockcroft-Gault calculation (77, 78).

Diabetes prevalence differed among studies. All of the patients in the NEPHRIC trial had diabetes mellitus in addition to renal impairment (23), compared with only 23.5% of those in the IMPACT trial (21) and 35.5%-41.4% in 3 of the 4 other studies (Tab. I) (19, 20, 22). Of note, in the ACTIVE trial, the incidence of diabetes in the overall population was lowest, at 20.1%, but there were more than twice as many patients with diabetes randomized to iomeprol compared with iodoxanol, representing a significant difference in baseline demographics between the 2 study arms (27.6% vs. 12.5%; p=0.02) (18) (Tab. I). Are differences like these important?

Two trials (both comparing bicarbonate and saline volume expansion) (29, 31) objectively evaluated the risk of CIN in the randomized study arms by applying a reported risk scoring system that assessed the relative contribution of 8 different risk factors for CIN observed in percutaneous coronary intervention populations (12). Based on individual patient data, both study populations were characterized by a risk score of 9, predictive of a moderate, 14%, CIN incidence according to the risk scoring system used (score 6-10 = 14%) (Tab. III). Can risk-scoring systems developed for individual patients be applied to derive a “population risk score” from reported demographic and clinical data and can this objective parameter then be compared across trials to consider the impact of different degrees of CIN risk on study outcomes? As illustrated for the trials that compared iodoxanol and various LOCMs, the studies that either failed to detect a difference in CIN incidence between iodoxanol and LOCM (19-21) or that found in favor of LOCM (18) tended to involve populations at the lower end of the risk-score spectrum, whereas a clear benefit in favor of iodoxanol was observed for high-risk study populations (22, 23) (Fig. 3).

Study protocol factors

The absence of clear evidence-based directions to date regarding CM safety or optimized volume expansion or NAC use understandably leads to study protocols with little consistency across trials and, therefore, questions as to which elements may or may not be confounding. Among the NAC trials, all except 1 (39) report the use of volume expansion as part of the protocol, but the type of fluid, volume, timing and route of administration are not standard across trials. The CM used in any one trial reflects the spectrum of choices available, with LOCM or IOCM predominating; in some cases, multiple types of CM were used in a single study (35, 42, 55) (Tab. IV). These same issues were present among the trials investigating other pharmacologic agents for CIN prophylaxis (Tab. V).

Among the 6 trials comparing iodoxanol and a LOCM, volume expansion protocols varied widely; in the 2 studies involving CT patients, approximately 65% and 88% of patients, respectively, did not receive fluid (18, 21), while in the NEPHRIC study, patients were repleted according to local protocol (23). Although patients in the Cardiac Angiography in Renally Impaired Patients (CARE) trial experienced the lowest rates of CIN among the trials conducted in the coronary angiography setting, use of bicarbonate for volume expansion in all patients may have contributed to the lower-than-expected CIN incidence and may have obscured potential differences between the agents (19). Use of NAC was not consistently reported among the trials comparing volume expansion strategies (Tab. II) or temporary renal replacement modalities (Tab. VI); NAC was not used in 2 of the 5 trials comparing bicarbonate and saline volume expansion (32, 33) (Tab. III). Among the trials comparing iodoxanol and LOCM, NAC was not permitted in some trials (18, 20-22), but was used in 8.5% of patients in the NEPHRIC study (23) and 40.6% in the CARE study (19) (Tab. I).

Variations in CM volume and/or iodine dose, as well as the potential impact of route of CM administration, need to be considered as sources of inconsistent findings within the trials. Large CM volumes and excessive iodine dosing are associated with increased CIN incidence (79, 80). Volumes <100 mL are recommended in individuals with renal impairment (GFR <60 mL/min per 1.73 m²) (81), as supported by recent findings demonstrating reduced CIN rates with the use of low CM volumes (iodixanol; 14 ± 4 mL to 34 ± 6 mL) in patients with CKD undergoing coronary angiography (82). In the trials comparing iodoxanol with LOCM, the mean CM volumes in the NEPHRIC and RECOVER trials were 163 mL and 205 mL of iodoxanol and 162 mL and 195 mL of the comparator LOCM, respectively (22, 23), compared with 136 mL iodoxanol and 134 mL iopamidol in the CARE trial (19). Volumes were lowest in the 2 CT trials, where CM was given intravenously at equal iodine dosing (125 mL iodoxanol and 108 mL iopamidol (21) or 100 mL iomeprol (18)). In the trial comparing iodoxanol and iopromide, CM volumes were not standardized, with some patients receiving up to 1,000 mL (20).

CIN in CT

Among the 54 studies identified, 8 involved the CT setting. CIN incidences of 21%-26% were observed for the control arms of trials investigating NAC use (34, 57) and prophylactic dialysis (70) in patients with CKD – indicating that CIN after CT can be a significant problem in this patient group. Considerable variation in practices for screening and pre-
vention exists among CT radiologists, and there is a need to more clearly define the risk factors for CIN in CT through studies using the protocols unique to that setting (83).

Features of the “ideal” CIN trial

In view of the various potential sources for inconsistency among different CIN trials, what features should be incorporated into an “ideal” trial?

CIN: definition

The need for a universally accepted definition of CIN is clear. A complete definition of CIN requires 3 components: a rise in SCr, a temporal relationship between that rise and exposure to CM, and exclusion of alternative explanations for the rise (84). For example, in the interventional cardiology setting a postprocedural increase in SCr could well reflect CIN but could also reflect worsening renal function secondary to cholesterol embolization.

The definition should not be so restrictive that a falsely low incidence of CIN results, otherwise the trial will have low power of discrimination; equally, the definition should not encompass so many patients that it loses clinical relevance. For a given population, the incidence of CIN is lower when defined as an absolute, ≥0.5 mg/dL, rather than a relative, ≥25% increase in baseline SCr. The relative measure is probably not appropriate for patients who do not have an increased baseline SCr; an increase in SCr from 0.6 mg/dL to 0.75 mg/dL, for example, although it is an increase of 25%, is unlikely to be of clinical importance (85).

Use of a lower value increment permits a smaller study sample size. One analysis has suggested that to observe a reduction in CIN of 40% resulting from a hypothetical intervention, lowering the defined SCr increment from ≥0.5 mg/dL to ≥0.25 mg/dL reduced the number of patients required in each of 2 study arms from >1,400 to 537 (3). Increments in SCr as low as 0.25-0.5 mg/dL have been associated with increased mortality and prolonged hospitalization, suggesting that a definition of CIN based on a ≥0.25 mg/dL threshold would identify clinically relevant effects (3). The move to replace the term CIN with contrast-induced acute kidney injury (AKI) is of note in this regard, given the 0.3 mg/dL (26.5 μmol/L) threshold SCr increase that is one component of the definition of AKI (86-88).

How should CIN be assessed?

Baseline SCr should be established before i.v. volume expansion, to avoid the fall in SCr induced by volume expansion (89). Furthermore, baseline SCr should be stable, based on at least 2 preprocedure determinations, with the latest 1 measured as close to the day of the procedure as possible. Since the renal response to CM varies in terms of timing and magnitude, postprocedure SCr measurements made at fixed rather than random time points will provide the most robust data. Ideally, several postprocedure SCr values should be acquired, daily from 24-72 hours postcontrast. If multiple determinations are not possible, then a single, fixed-time SCr measure could be used for all subjects; SCr determination at 48 hours would appear to be the most representative of CIN occurrence in a given population (76). Where an acute change is detected, SCr measurements should continue until the peak has passed.

Although an increase in SCr is a widely used and practical means by which to detect CIN in clinical trials, it has several limitations. Notably, changes in SCr underestimate the true fall in GFR and lag 24-48 hours behind the CM-induced fall in GFR (89). Estimation equations based on SCr are known to perform poorly, compared with direct GFR measurement by radionuclide clearance, for assessment of changes in renal function in acutely ill, hospitalized patients who commonly require multiple contrast studies and are at particularly high risk of CIN due to the presence of confounding morbidities (90). Other markers of renal function such as cystatin C (or newer markers of AKI) may provide a more accurate measure of CM-induced renal impairment than SCr (37). Finally, because trials to date have primarily focused on assessment of changes in kidney function over a short time period, CIN as defined in these trials may not correlate with serious clinical outcomes. An ideal clinical trial of CIN, therefore, would involve a primary end point with a hard clinical outcome measure, such as the incidence of required renal replacement therapy.

The study population

As CIN risk is low in the general population, inclusion of patients with normal kidney function in a trial will increase the size of the study population required for adequate statistical power and produce a low rate of CIN. The risk of CIN is higher and clinically relevant when baseline SCr is ≥1.3 mg/dL for men and ≥1.0 mg/dL for women, corresponding to an estimated GFR <60 mL/min per 1.73 m² (91). Trials should include only patients with CKD, as evidenced by a stable baseline (prior to volume expansion) SCr >1.5 mg/dL or an estimated GFR of <60 mL/min per 1.73 m², to ensure the risk of CIN is sufficient for any prophylactic effect to be realized. Whether diabetes mellitus should also be an inclusion criterion is a matter of debate. While this limitation would restrict the extent to which findings could be generalized, it would also be expected to increase the CIN event rate, and hence the power to detect a significant difference between study arms, because of the increased risk of CIN when diabetes presents in association with CKD.
Study protocol

Best practice volume expansion should be incorporated into any CIN trial. All fluids should be isotonic (28). Bicarbonate-based strategies merit consideration based on the RCTs identified here, all of which consistently demonstrate a significant benefit in favor of bicarbonate (29-33) (Tab. III). A recent large retrospective analysis reporting an increased incidence of CIN associated with bicarbonate-based volume expansion is of interest, but the strength of these findings awaits confirmation from future RCTs (92). The duration of the ideal volume expansion protocol remains to be established, and, in the absence of evidence from controlled trials to the contrary, short protocols may be preferred because they enable more efficient bed usage. Based on bicarbonate protocols, where volumes ranged from 600 to 1,700 mL (29-33), a reasonable recommendation would be a bolus injection of 3 to 5 mL/kg over 1 hour before CM administration, followed by 1 mL/kg per hour for 12 hours, resulting in a total volume of 1,000-1,200 mL – which is usually well-tolerated in all patients. Because data regarding NAC are inconsistent, inclusion of NAC for CIN prevention in an ideal study protocol is currently without any basis of support.

The extent to which volume expansion and pharmacologic measures obviate the nephrotoxic effects of CM is uncertain because of the inconsistencies between trials and absence of clear findings. It could be argued that trials where greater attention was paid to such issues, as in the recent CARE trial, which incorporated the newer findings regarding bicarbonate (19), resulted in lower incidence of CIN, but, as discussed, other differences between trials, such as disparate population risk profiles, complicate comparisons.

Conclusions

The clinical community recognizes the serious prognostic implications of CIN, and this awareness is reflected in the large number of CIN-related studies in the medical literature. Large, well-designed trials, ideally with hard clinical outcome measures, that consider all the complexities involved in CIN and its prevention are needed before the clinical community has the evidence-based direction required for optimized patient care. Whether future CIN trials are investigating the comparative nephrotoxicity of contrast agents or dealing with prophylactic strategies for risk reduction, the complexities that must be addressed include a standardized definition of CIN, appropriate timing of SCR measurements with timing standardized for all subjects in a given study, awareness of study population risk profile, volume expansion protocols and pharmacologic prophylactic strategies.

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