

# Strategies to Reduce the Risk of Contrast-Induced Nephropathy

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In view of the clinical importance of contrast-induced nephropathy (CIN), numerous potential risk-reduction strategies have been evaluated. Adequate intravenous volume expansion with isotonic crystalloid (1.0–1.5 mL/kg per hr) for 3–12 hours before the procedure and continued for 6–24 hours afterward can lessen the probability of CIN in patients at risk. There are insufficient data on oral fluids (as opposed to intravenous volume expansion) as a CIN-prevention strategy. No adjunctive medical or mechanical treatment has been proved to be efficacious in reducing risk for CIN. Prophylactic hemodialysis and hemofiltration have not been validated as effective strategies. The CIN Consensus Working Panel considered that, of the pharmacologic agents that have been evaluated, theophylline, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), ascorbic acid, and prostaglandin E<sub>1</sub> deserve further evaluation. *N*-acetylcysteine is not consistently effective in reducing the risk for CIN. Fenoldopam, dopamine, calcium channel blockers, atrial natriuretic peptide, and L-arginine have not been shown to be effective. Use of furosemide, mannitol, or an endothelin receptor antagonist is potentially detrimental. Nephrotoxic drugs should be withdrawn before contrast administration in patients at risk for CIN. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;98[suppl]:59K–77K)

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In view of the frequency with which contrast-induced nephropathy (CIN) occurs in patients at risk, the impact of postprocedure renal impairment on healthcare costs, and the adverse effects of CIN on long-term prognosis, numerous strategies have been evaluated for their potential to reduce the risk of postprocedure increases in serum creatinine. Many investigators have undertaken clinical trials of clinical procedures and pharmacologic agents intended to reduce the risk for CIN. However, the results often have been disappointing or inconsistent, and intravenous volume expansion is the only strategy that has been shown consistently to reduce the risk for CIN. This review provides an overview of the results of the main clinical trials identified by a literature search and offers guidance on the most realistic approaches to reducing the risk for CIN in routine clinical practice. The CIN Consensus Working Panel agreed on 2 consensus statements on preventive strategies to reduce the risk for CIN.

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## Consensus Statements

**Consensus statement 9:** Adequate intravenous volume expansion with isotonic crystalloid (1.0–1.5 mL/kg per hour) for 3–12 hours before the procedure and continued for 6–24 hours afterward can lessen the probability of CIN in patients at risk. The data on oral fluids as opposed to intravenous volume expansion as a CIN prevention measure are insufficient.

**Consensus statement 10:** No adjunctive medical or mechanical treatment has been proved to be efficacious in reducing the risk of CIN. Prophylactic hemodialysis or hemofiltration has not been validated as an effective strategy.

## Volume Expansion and Hydration

Volume expansion has a well-established role in reducing the risk for CIN, though few studies address this theme directly. Many patients described in early case reports of CIN were dehydrated.<sup>1–5</sup> This applied particularly to patients undergoing intravenous urography, because fluid restriction was a common strategy to increase the concentration of contrast medium in the urine. Early uncontrolled studies suggested that adequate volume expansion can reduce the incidence and severity of CIN.<sup>6,7</sup> An uncontrolled study in 214 patients suggested that an infusion of 1,000 mL saline 0.45% with mannitol, furosemide, and sodium bicarbonate reduced the risk for CIN and led the authors to recommend that a controlled trial was needed.<sup>8</sup> However, there have been no randomized controlled trials directly

comparing a strategy of volume expansion with no volume expansion.

It is not clear exactly how volume expansion reduces the risk for CIN. Although the exact mechanisms for the protective effects of intravenous fluid administration are unknown, vigorous volume expansion could reduce CIN through a number of potential mechanisms, including the following:

1. Intravenous administration of half-normal (0.5 N) saline 0.45% may cause an increase in free water excretion, leading to dilution of the contrast agents within the tubule lumen. This form of prophylaxis could reduce the likelihood of tubular precipitation of contrast agents and prevent intraluminal obstruction from necrotic epithelium or act by other potential mechanisms
2. Intravenous volume expansion with normal saline has been shown to be superior to 0.5 N saline hydration.<sup>9</sup> Its potential beneficial effects may involve increased delivery of sodium to the distal nephron, leading to reduced activation of the renin-angiotensin system via the macula densa. Reducing renin activation and the attendant "prerenal" physiology would allow renal blood flow to remain above the threshold that leads to overt tubular necrosis. However, it is important to note that no single threshold for all patients has been identified
3. Intravenous volume expansion would also minimize reductions in the renal production of nitric oxide. Animal model studies demonstrate that noniodinated high-osmolarity solutions reduce the autoregulatory capacity of the renal vasculature through a loss of nitric oxide production. (See the article by Tumlin and associates in this supplement.<sup>10</sup>)

Most recent clinical trials of pharmacologic agents for CIN prophylaxis have used adjunctive intravenous 0.5 N saline 0.45%. However, there are limited data on the most appropriate choice of intravenous fluid (Table 1).<sup>9,11-15</sup> The trial by Mueller and colleagues<sup>9</sup> randomized 1,620 patients to receive either saline 0.9% or saline 0.45%, 1 mL/kg per hr for 24 hours beginning early on the day of angioplasty. The incidence of CIN (increase in serum creatinine of  $\geq 0.5$  mg/dL [ $44.2 \mu\text{mol/L}$ ] within 48 hours) was significantly lower with saline 0.9% than with saline 0.45% (0.7% vs 2%;  $p = 0.04$ ).<sup>9</sup> In another randomized trial in 119 patients, intravenous sodium bicarbonate was compared with sodium chloride (154 mEq/L of each, given as 3 mL/kg per hr for 1 hour before and 1 mL/kg per hr for 6 hours after the procedure). This showed that the risk for CIN (increase of  $\geq 25\%$  in serum creatinine within 48 hours) was significantly lower in the group receiving bicarbonate (1.7% vs 13.6%,  $p = 0.02$ ).<sup>11</sup> The CIN Consensus Working Panel considered that isotonic saline was the most appropriate intravenous fluid for use at the present time and that further studies of sodium bicarbonate are required. It has been

speculated that alkalinizing the urine reduces the nephrotoxicity of iodinated contrast media through changes in redox potential or through decreasing the viscosity of the agents within the vasa recta. The CIN Consensus Working Panel concluded that additional confirmatory trials with bicarbonate must be performed before a conclusive protective mechanism can be identified.

There is also no clear evidence to guide the choice of the optimal rate and duration of infusion. A prospective randomized study showed that intravenous volume expansion ( $\geq 2,000$  mL saline over 12 hours before and after contrast exposure) was more effective than a 300-mL saline bolus during contrast administration as shown by the significantly ( $p < 0.05$ ) lower decline in glomerular filtration rate (GFR). The incidence of CIN was also lower.<sup>12</sup> Another randomized trial also showed a trend toward a lower incidence of CIN with overnight intravenous fluid compared with bolus administration.<sup>13</sup>

Overnight intravenous volume expansion is not possible for outpatients, and several investigators have evaluated the role of oral regimens. One study showed that an outpatient protocol including oral fluids (1,000 mL clear liquid over 10 hours) followed by 6 hours of intravenous fluid (saline 0.45% solution at 300 mL/hr) beginning just before the procedure was as effective as overnight intravenous fluid (saline solution 0.45% at 75 mL/hr for 12 hours before and after catheterization).<sup>14</sup> However, in this trial, the oral regimen was compared with intravenous saline 0.45%, which may be less effective than normal saline. A randomized trial in 53 patients showed that the incidence and severity of CIN was lower in patients who received normal saline intravenously at a rate of 1 mL/kg per hr for 12 hours before and after the procedure than in those who received unrestricted oral fluids.<sup>15</sup> The CIN Consensus Working Panel agreed that oral fluid administration may have some benefit, but there is not enough evidence to show that it is as effective as intravenous volume expansion.

**Protocols for intravenous fluid:** Table 1 summarizes the protocols that have been used in clinical trials of volume expansion.<sup>9,11-15</sup> The majority of studies have been carried out in patients undergoing cardiac catheterization. After reviewing the evidence, the CIN Consensus Working Panel agreed that the optimum protocol to reduce the risk for CIN is 1–1.5 mL/kg per hr of intravenous isotonic crystalloid initiated 12 hours before the procedure and continued for 6–24 hours afterward—a regimen that is achievable in hospitalized patients. However, this regimen is impractical for outpatients. They should receive intravenous crystalloid for up to 3 hours before the procedure and for up to 12 hours afterward, depending on the timing of the procedure and the expected discharge time. The CIN Consensus Working Panel considered that adequate postprocedure volume expansion may be even more important than preprocedure fluids. So far, 2 prospective trials in patients receiving contrast agents have examined the duration of the reduction

Table 1  
Clinical trials of volume expansion protocols

| Study                        | Aim  | Patients, N<br>(Group 1/Group 2) | Group 1  |  | Group 2  |  | CIN Definition                       | CIN Incidence |         |         |
|------------------------------|--|----------------------------------|--|--|--|--|--------------------------------------|---------------|---------|---------|
|                              |  |                                  | Preprocedure Regime  | Postprocedure Regime                                 | Preprocedure Regime  | Postprocedure Regime   |                                      | Group 1       | Group 2 | p Value |
| Mueller et al <sup>9</sup>   | Isotonic vs half-isotonic saline   | 809/811                          | Saline 0.9% at 1 mL/kg/hr IV started at 8 AM on morning of angioplasty | Saline 0.9% at 1 mL/kg/hr IV until 8 AM next morning | Saline 0.45%/glucose 5% at 1 mL/kg/hr IV started at 8 AM on morning of angioplasty                   | Saline 0.45%/glucose 5% at 1 mL/kg/hr IV until 8 AM next morning | ≥0.5 mg/dL SCr increase within 48 hr | 0.70%         | 2.00%   | 0.04    |
| Merten et al <sup>11</sup>   | NaHCO <sub>3</sub> vs NaCl infusion  | 60/59                            | NaHCO <sub>3</sub> 154-mEq/L infusion at 3 mL/kg IV for 1 hr           | NaHCO <sub>3</sub> at 1 mL/kg/hr IV for 6 hr         | NaCl 154-mEq/L infusion at 3 mL/kg IV for 1 hr   | NaCl at 1 mL/kg/hr IV for 6 hr                                   | 25% SCr increase within 48 hr        | 1.70%         | 13.60%  | 0.02    |
| Bader et al <sup>12</sup>    | Comparison between overnight and bolus infusion  | 19/20                            | Saline 1,000 mL IV over 12 hr  | Saline 1,000 mL IV over 12 hr                        | 300-mL saline bolus during CM administration   |  | 50% decrease in GFR within 48 hr     | 5.30%         | 15%     | 0.605   |
| Krasuski et al <sup>13</sup> | Comparison between overnight and bolus infusion  | 26/37                            | Saline 0.45%/dextrose 5% at 1 mL/kg/hr IV for 12 hr                    | Saline 0.45%/dextrose 5% at 1 mL/kg/hr IV for 12 hr  | 250-mL saline 0.9% IV over 20 min  | Saline 0.45%/dextrose 5% at 1 mL/kg/hr IV for 12 hr              | ≥0.5 mg/dL SCr increase within 48 hr | 0             | 10.80%  | 0.136   |
| Taylor et al <sup>14</sup>   | Comparison between overnight IV infusion and outpatient oral precatheterization strategy | 18/18                            | Saline 0.45% at 75 mL/hr IV for 12 hr                                  | Saline 0.45% at 75 mL/hr IV for 12 hr                | 1,000 mL water PO over 10 hr followed by saline 0.45% at 300 mL/hr IV for 30–60 min before procedure | Saline 0.45% at 300 mL/hr IV for total of 6 hr                   | ≥0.5 mg/dL SCr increase within 48 hr | 11.10%        | 5.60%   | NR      |
| Trivedi et al <sup>15</sup>  | Comparison between overnight infusion and unrestricted oral fluids                       | 27/26                            | Saline 0.9% at 1 mL/kg/hr IV for 12 hr                                 | Saline 0.9% at 1 mL/kg/hr IV for 12 hr               | Unrestricted oral fluids   | Unrestricted oral fluids   | ≥0.5 mg/dL SCr increase within 48 hr | 3.70%         | 34.60%  | 0.005   |

CIN = contrast-induced nephropathy; CM = contrast medium; GFR = glomerular filtration rate; IV = intravenous; NR = not reported; PO = orally; SCr = serum creatinine.

in renal blood flow following contrast exposure. Russo and associates<sup>16</sup> noted that renal blood flow remains 30% below baseline levels for up to 2 hours. In a similar, but longer, duration study, Tumlin and coworkers<sup>17</sup> directly measured renal blood flow in 51 patients undergoing cardiac catheterization and noted that renal blood flow was reduced by up to 50% 4 hours after contrast infusion. Because the precise duration of vasoconstriction is unknown, the CIN Consensus Working Panel recommended that intravenous saline administration be maintained for up to 12 hours after contrast infusion to reduce alterations in renal blood and thereby reduce the incidence of CIN.

The CIN Consensus Working Panel agreed that it is not useful to recommend a target urine output. The Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE) trial suggested that there was a modest benefit from a forced diuresis regime with maintenance of intravascular volume in patients who achieved high urine flow rates,<sup>18</sup> but there are no other trial results to confirm this finding.

The CIN Consensus Working Panel considered the concerns that have been expressed about the possible risks of fluid overload and pulmonary edema, associated with infusion of large volumes of fluid in patients with impaired left ventricular function. Occasional cases have been reported in the literature,<sup>6,13</sup> and a 5% incidence of pulmonary edema was reported in 1 study with *N*-acetylcysteine (NAC).<sup>19</sup> However, patients with congestive heart failure (CHF) or pulmonary edema are often excluded from clinical trials of CIN prevention; hence there is a very limited evidence base to guide practice. The CIN Consensus Working Panel agreed that caution is needed in patients with CHF but considered that the risk of volume overload may be lower than is often believed. If it occurs, it can be managed relatively easily. In outpatients with compensated CHF, fluid should be infused at a lower rate. In cardiac patients, hemodynamic measurements are feasible and consideration should be given to using them to guide the postprocedure infusion rate. In patients with uncompensated CHF, the CIN Consensus Working Panel recommended that consideration should be given to right heart catheterization for hemodynamic monitoring, with the infusion rate adjusted appropriately. Diuretics should be continued.

**Emergency situations:** In an emergency situation full preprocedure volume expansion is not possible, and there is a lack of published evidence to guide clinicians about appropriate alternatives. The CIN Consensus Working Panel agreed that in emergency situations, where the potential benefit from an urgent investigation outweighs the risks of waiting, the procedure can be undertaken without knowledge of renal function, which precludes risk stratification according to renal function. Hence, clinical judgment is needed. Appropriate postprocedure intravenous fluids should be given.

## Hemodialysis

Dialysis is effective in removing contrast medium.<sup>20–23</sup> However, randomized trials of prophylactic hemodialysis showed that it is not effective in reducing the risk for CIN,<sup>24,25</sup> even when carried out within 1 hour<sup>26</sup> or simultaneously with contrast administration.<sup>27</sup> In a study of 17 patients with advanced chronic kidney disease, Frank and coworkers<sup>27</sup> simultaneously hemodialyzed patients during cardiac catheterization and demonstrated that hemodialysis effectively reduces contrast levels in the blood. However, despite its ability to clear these agents, the incidence of CIN was not reduced at 1 week or 8 weeks after contrast exposure. These observations are consistent with previous animal studies demonstrating the rapid effects of contrast agents on renal blood flow and imply that renal damage occurs very rapidly. In 1 study, there was a trend for more complications in the hemodialysis group.<sup>28</sup>

Although hemodialysis is not useful for reducing the risk for CIN, the CIN Consensus Working Panel agreed that for patients with severe renal impairment (estimated GFR [eGFR] <20 mL/min) who require contrast medium administration, preparation for the procedure should include planning for hemodialysis in the event that CIN occurs despite appropriate precautions.

## Hemofiltration

One study in 114 patients showed that in patients with severe chronic renal impairment (serum creatinine >2 mg/dL [ $>176.8 \mu\text{mol/L}$ ]), continuous venovenous hemofiltration (1,000 mL/hr without weight loss) was more effective than intravenous volume expansion in reducing the risk for CIN (normal saline 1 mL/kg per hr). Hemofiltration and intravenous volume expansion were both started 4–8 hours before percutaneous coronary intervention (PCI) and continued for 18–24 hours afterward. It is important to note that CIN was defined in this study as a >25% increase in serum creatinine; this occurred less frequently in the group receiving hemofiltration than in the group treated with volume expansion (5% vs 50%;  $p < 0.001$ ). However, because the intervention of hemofiltration itself affected the serum creatinine level, it cannot be determined whether there was a beneficial effect of hemofiltration. Although the in-hospital and 1-year mortality were significantly lower in the patients who underwent hemofiltration, the flawed nature of the trial design does not allow for definitive conclusions regarding this technique.<sup>29</sup> The CIN Consensus Working Panel considered that hemofiltration deserves further investigation using end points unaffected by the experimental intervention, but the high cost and need for intensive care unit admission will also limit the utility of this prophylactic approach.

## Pharmacologic Agents

The CIN Consensus Working Panel reviewed published reports describing various pharmacologic agents evaluated for reduction of the risk for CIN. Many of the trials have given negative or conflicting results, and there are no drugs with robust and consistent trial evidence to support clinical use in patients at risk for CIN. The majority of clinical trials of potentially protective agents have been undertaken in patients receiving intra-arterial contrast medium, for PCI/coronary angiography in most cases, and there are very few trials in patients receiving intravenous contrast media. Moreover, no drugs are approved by regulatory authorities anywhere in the world for prevention of CIN.

For most of the pharmacologic agents that have been evaluated for reduction in the risk for CIN, the rationale for use has been based on current understanding of the pathogenesis of CIN. Thus, 3 main groups have been assessed: vasodilators, antagonists of intrarenal mediators, and cytoprotective agents.

After reviewing the evidence, the CIN Consensus Working Panel divided the drugs that have been evaluated in patients at risk for CIN into 3 categories based on their results (Table 2).

**Positive results:** These are potentially beneficial agents that need further evaluation but could be considered for use in patients at risk.

**THEOPHYLLINE/AMINOPHYLLINE.** Because adenosine is an intrarenal vasoconstrictor and a mediator of the tubuloglomerular feedback mechanism, it was logical to evaluate adenosine antagonists for risk reduction in CIN. A total of 11 studies were identified that evaluated adenosine antagonists in patients at risk for CIN (Table 3).<sup>30–40</sup> Of the 11 studies, 9 were randomized controlled trials (8 with theophylline, 1 with aminophylline)<sup>30–38</sup> and 2 were case-control studies (1 with aminophylline).<sup>39,40</sup> There appears to be some overlap between patients included in 2 of the reports.<sup>34,35</sup> Various oral and intravenous dosage regimens have been evaluated, but a single intravenous dose before the procedure is a convenient option.

Whereas 3 of the controlled trials showed a significant reduction in the risk for CIN,<sup>34–36</sup> another 3 studies showed no reduction.<sup>30,32,33</sup> Although CIN was not an end point in the other 3 trials, less decline in renal function was observed in patients receiving theophylline.<sup>31,37,38</sup> A meta-analysis of 7 trials (N = 480) showed that the administration of theophylline or aminophylline had a statistically significant effect on the decline in renal function after contrast medium administration.<sup>41</sup> The CIN Consensus Working Panel considered that these results were sufficiently positive for clinicians to consider the prophylactic use of theophylline in patients at high risk for CIN, although further studies are required to validate this contention. The potential benefits of theophylline must be weighed against the narrow therapeutic

Table 2

Pharmacologic agents evaluated for contrast-induced nephropathy risk reduction

- 
- Positive results (potentially beneficial)
    - Theophylline/aminophylline
    - Statins
    - Ascorbic acid
    - Prostaglandin E<sub>1</sub>
  - Neutral results (no consistent effect)
    - N-acetylcysteine
    - Fenoldopam
    - Dopamine
    - Calcium channel blockers
      - Amlodipine
      - Felodipine
      - Nifedipine
      - Nitrendipine
    - Atrial natriuretic peptide
    - L-Arginine
  - Negative results (potentially detrimental)
    - Furosemide
    - Mannitol
    - Endothelin receptor antagonist
- 

index and potential for serious adverse effects including gastrointestinal, neurological, and cardiovascular effects.<sup>42</sup>

**STATINS.** It has been suggested that the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, may reduce the risk for CIN<sup>43</sup> because they have beneficial effects on endothelial function, maintain nitric oxide production, and reduce oxidative stress.<sup>44</sup> A retrospective review of 1,002 patients with renal impairment (baseline serum creatinine  $\geq 1.5$  mg/dL [ $\geq 132.6$   $\mu\text{mol/L}$ ]) undergoing coronary angiography suggested that the risk for CIN was lower in patients in whom a statin was initiated just before the procedure. A 50% increase in serum creatinine occurred in 17.2% of the 250 patients receiving statins and in 22.3% of the 752 patients in the control group ( $p = 0.028$ ).<sup>43</sup> The results of a large PCI registry study published since the literature search for this review also support this conclusion,<sup>45</sup> and the CIN Consensus Working Panel considered that these findings were of such importance for clinicians that this report should be included. Records of 29,409 patients were reviewed and the results showed that, compared with patients who did not receive statin therapy, patients who received statins before their procedure had a lower incidence of both CIN and nephropathy requiring dialysis. The incidence of CIN, defined as an increase in serum creatinine of  $\geq 0.5$  mg/dL ( $\geq 44.2$   $\mu\text{mol/L}$ ), was 4.37% in the statin group and 5.93% in the nonstatin group ( $p < 0.0001$ ); the incidence of nephropathy requiring dialysis was 0.32% in the statin group and 0.49% in the nonstatin group ( $p = 0.03$ ).<sup>45</sup> These data reinforce the rationale for the introduction of statin therapy before PCI. However, there is not enough evidence to support the use of statins in radiology patients in whom these drugs are not otherwise indicated.

Table 3  
Theophylline/aminophylline trials\*

| Study                       | Aim  | Patients (N)  | Patient Type   | Procedures   | Theophylline/<br>Aminophylline<br>Dose   | Placebo/Control<br>Dose | Route of<br>Administration | CIN<br>Definition  | CIN Incidence                  |                           | p<br>Value                        | Outcomes  | Conclusions  |
|-----------------------------|--|---|--|--|--|-------------------------|----------------------------|--|--------------------------------|---------------------------|-----------------------------------|---|--|
|                             |  |   |  |  |  |                         |                            |  | Theophylline/<br>Aminophylline | Control                   |                                   |   |  |
| Abizaïd et al <sup>30</sup> | RCT<br>(aminophylline<br>vs dopamine<br>vs saline) | 60: 20/group  | SCr $\geq 1.5$ mg/dL   | PCI  | Aminophylline<br>4 mg/kg<br>followed by<br>0.4 mg/kg/hr,<br>2 hr before<br>and 12 hr after<br>procedure                                  | Saline                  | IV                         | $\geq 25\%$<br>increase in<br>SCr <sup>†</sup>   | 35%                            | Saline<br>30%             | NS                                | Length of stay, peak SCr,<br>change in SCr, time to peak<br>SCr, dialysis: NS between the<br>3 groups   | Aminophylline is not<br>superior to saline<br>alone  |
| Erley et al <sup>31</sup>   | RCT  | 39: 19<br>theophylline,<br>20 control                               | Mean SCr 1.2<br>mg/dL; 43%<br>with GFR $< 75$<br>mL/min/1.72 m <sup>2</sup>  | CT or digital<br>subtraction<br>angiography  | Theophylline 5<br>mg/kg, 45 min<br>preprocedure  | Placebo (saline)        | IV                         | —  | —                              | —                         | —                                 | Change in GFR: significant<br>decline in the placebo group<br>from 88 to 75 mL/min<br>( $p < 0.01$ ), but not the<br>theophylline group   | Theophylline can<br>prevent CM-<br>induced decrease<br>in GFR in patients<br>with/without RI                                       |
| Erley et al <sup>32</sup>   | RCT  | 80: 64<br>completed<br>protocol (35<br>theophylline,<br>29 control) | SCr $> 1.5$ mg/dL  | CT or digital<br>subtraction<br>angiography  | Theophylline 810<br>mg/day (270<br>mg in the<br>morning, 540<br>mg in the<br>evening), 2<br>days before<br>and 3 days<br>after procedure | Placebo                 | PO                         | 0.5 mg/dL<br>increase in<br>SCr <sup>†</sup>   | 5.70%                          | 3.40%                     | NS                                | Change in SCr, change in CrCl:<br>NS in both groups; NAG<br>excretion: increase in both<br>groups, but significant<br>( $p < 0.05$ ) in the placebo<br>group only, on days 2 and 3  | Oral/IV fluid<br>preserved renal<br>function, with no<br>further benefit<br>from theophylline                                      |
| Gandhi et al <sup>33</sup>  | RCT  | 21: 13<br>theophylline,<br>8 control                                | CrCl 86.9 mL/<br>min, placebo;<br>89.7 mL/min<br>theophylline  | Coronary<br>angiography  | Theophylline 125<br>mg tid, 24 hr<br>before and 48<br>hr after<br>procedure  | Placebo                 | PO                         | Significant<br>renal<br>impairment<br>(not<br>specified)                               | 15%                            | 12.50%                    | NS                                | Change in CrCl: NS in both<br>groups (stable, compared with<br>baseline, in both groups)  | No evidence of<br>protective effect of<br>theophylline with<br>this dose (125 mg<br>tid) in a small<br>group of patients           |
| Huber et al <sup>34</sup>   | RCT  | 100: 50<br>theophylline,<br>50 control                              | SCr $\geq 1.3$ mg/dL   | Various, 54<br>coronary<br>angiography,<br>24 CT, 12<br>iliofemoral<br>arteriography | Theophylline 200<br>mg, 30 min<br>preprocedure   | Placebo (saline)        | IV                         | $\geq 0.5$ mg/dL<br>increase in<br>SCr at 48<br>hr                                     | 4%                             | 16%                       | 0.046                             | Change in SCr at 24 hr:<br>theophylline, NS decrease<br>from 2.07 to 1.97 mg/dL ( $p =$<br>0.99); placebo, significant<br>increase from 1.92 to 2.01<br>mg/dL ( $p = 0.006$ )   | Prophylactic<br>administration of<br>200 mg<br>theophylline<br>reduces the<br>incidence of CIN<br>in patients with RI              |
| Huber et al <sup>35</sup>   | RCT  | 100: 50<br>theophylline,<br>50 control                              | SCr $\geq 1.3$ mg/dL   | Coronary<br>angiography  | Theophylline 200<br>mg, 30 min<br>preprocedure   | Placebo (saline)        | IV                         | $\geq 0.5$ mg/dL<br>increase in<br>SCr at 48<br>hr                                     | 4%                             | 20%                       | 0.0138                            | Change in SCr at 48 hr:<br>theophylline, stable (1.65 mg/<br>dL NS); placebo, significant<br>increase over baseline (from<br>1.72 to 1.9 mg/dL, $p =$<br>0.0007)  | Prophylactic<br>administration of<br>200 mg<br>theophylline<br>reduces the<br>incidence of CIN<br>in patients with RI              |
| Kapoor et al <sup>36</sup>  | RCT  | 70: 35<br>theophylline,<br>35 control                               | Diabetes mellitus<br>and SCr $< 3.0$<br>mg/dL; mean<br>GFR: control<br>85.4 mL/min,<br>theophylline<br>86.8 mL/min | Coronary<br>angiography  | Theophylline 200<br>mg bid, for 24<br>hr before and<br>48 hr after<br>procedure  | No drug                 | PO                         | $\geq 25\%$<br>increase in<br>SCr or<br>$\geq 25\%$<br>decrease in<br>GFR <sup>†</sup> | SCr 0%;<br>GFR 3%              | SCr<br>20%;<br>GFR<br>31% | 0.017<br>(SCr);<br>0.004<br>(GFR) | Change in SCr: control group,<br>increase from 1.19 to 1.44<br>mg/dL ( $p = 0.03$ );<br>theophylline group, NS.<br>Change in GFR: control<br>group, decrease from 85.4 to<br>66.8 mL/min ( $p = 0.008$ );<br>theophylline group, NS   | Prophylactic<br>administration of<br>200 mg bid<br>theophylline<br>reduces the<br>incidence of CIN<br>in patients with<br>diabetes |
| Katholi et al <sup>37</sup> | RCT  | 93: 47<br>theophylline,<br>46 control                               | SCr $< 2.0$ mg/dL  | Coronary<br>angiography/<br>left ventri-<br>culography                               | Theophylline<br>2.88 mg/kg,<br>every 12 hr $\times$<br>4; first dose at<br>$\geq 1$ hr<br>preprocedure                                   | Placebo                 | PO                         | —  | —                              | —                         | —                                 | Change in CrCl at 24 hr:<br>significant decrease in the<br>placebo-iopamidol group<br>(18%, from 82 to 68 mL/min,<br>$p < 0.05$ ), but not in the<br>theophylline-iopamidol group;<br>significant decrease in the<br>placebo-diatrizoate group<br>(42%, from 79 to 46 mL/min,<br>$p < 0.01$ ) and in the<br>theophylline-diatrizoate group<br>(24%, from 80 to 61 mL/min,<br>$p < 0.05$ ) | Supports the<br>hypothesis that<br>intrarenal<br>adenosine is<br>implicated in the<br>pathogenesis of<br>CIN                       |

Table 3  
(continued)

| Author                      | Study Design  | Intervention  | Control             | Primary Endpoints  | Secondary Endpoints                             | Significance                      | Notes   |
|-----------------------------|---|---|---------------------|--|---|-----------------------------------|---|
| Kolonko et al <sup>38</sup> | RCT   | Theophylline 165 mg, 30 min preprocedure                    | Placebo (saline) IV | SCR <1.4 mg/dL; CrCl 107.5 mL/min (placebo), 106.4 mL/min (theophylline) | Radiologic examinations                         | —                                 | Change in GFR: reduction in placebo patients, from 107.5 to 88.4 mL/min on day 1 (p <0.001), but not in patients treated with theophylline. Change in SCR: significant increase in the placebo group from 1–1.2 mg/dL (p <0.001), but not in the theophylline group |
| Huber et al <sup>39</sup>   | Comparison with historical series at comparable risk of CIN | Theophylline 200 mg/70 kg (2.86 mg/kg), 30 min preprocedure | NA                  | ICU patients with ≥1 risk factor for CIN                                 | Radiologic procedures including CT              | 2%                                | Published <0.0001 (cases vs controls 14% vs control series)   |
| Shammas et al <sup>40</sup> | Case-control study  | Aminophylline 200 mg, immediately before procedure          | NA                  | SCR ≥1.4 mg/dL   | Coronary and peripheral angiographic procedures | ≥25% increase in SCR <sup>†</sup> | Matched NS (cases vs matched controls) 11.5%  |

CIN = contrast-induced nephropathy; CM = contrast medium; CrCl = creatinine clearance; CT = computed tomography; GFR = glomerular filtration rate; ICU = intensive care unit; IV = intravenous; NA = not available; NAG = N-acetyl-β-glucosaminidase; NS = not significant; PCI = percutaneous coronary intervention; PO = oral; RCA = radiographic contrast agent; RCT = randomized controlled trial; RI = renal insufficiency; SCR = serum creatinine.  
 \* 1 mg/dL = 88.4 μmol/L.  
 † Time during which change took place not specified.

**ASCORBIC ACID.** In view of the possible role of oxidative stress and free radical production in CIN, ascorbic acid was assessed because it is a widely available and well-tolerated antioxidant with an extensive safety record as a dietary supplement. Oral ascorbic acid (3 g before and 2 g given 2 times after the procedure) was evaluated in a randomized, double-blind, placebo-controlled trial in 231 patients undergoing cardiac catheterization. The incidence of CIN, defined as ≥0.5 mg/dL (44.2 μmol/L) or a ≥25% increase in serum creatinine, was 9% in the ascorbic acid group and 20% in the placebo group (p = 0.02), representing a 62% reduction in risk.<sup>46</sup>

**PROSTAGLANDIN E<sub>1</sub> (PGE<sub>1</sub>).** Because renal vasoconstriction is believed to contribute to the pathogenesis of CIN, preliminary studies have been undertaken with vasodilator prostaglandins. Misoprostol (a PGE<sub>1</sub> analog), given as a dosage of 200 μg 4 times daily, initiated 3 days before, radiologic procedures and continued for 2 days afterward, attenuated the decline in creatinine clearance observed in the placebo group.<sup>47</sup> A pilot study with intravenous PGE<sub>1</sub> was designed to evaluate its role in reducing the risk for CIN and to determine the most appropriate dose. Patients with renal impairment (defined as serum creatinine ≥1.5 mg/dL [≥132.6 μmol/L]) undergoing coronary and peripheral angiography were randomized to 1 of 3 PGE<sub>1</sub> doses, 10, 20, or 40 ng/kg per min or placebo for 6 hours starting before the procedure. The increase in serum creatinine was less in each of the PGE<sub>1</sub> groups compared with placebo, with the difference being significant at the 20-ng/kg per min dose (p = 0.01).<sup>48,49</sup> There were no clinically relevant changes in calculated creatinine clearance in any group.<sup>48</sup> Clinically relevant decreases in blood pressure were observed in 23% of patients in the 40-ng/kg per min group and in 6.5% (placebo), 6.1% (10 ng/kg per min) and 5.6% (20 ng/kg per min) of the other groups.

**Neutral:** These are agents that have not been shown to be consistently effective in reducing the risk for CIN.

**NAC.** The possible role of reactive oxygen radicals in the pathogenesis of CIN led to the evaluation of NAC, an antioxidant. A total of 27 studies of varying quality evaluating NAC for CIN prophylaxis were identified by the literature search (Table 4).<sup>19,50–75</sup> Additionally, 9 published meta-analyses were identified, all documenting the significant heterogeneity between studies.<sup>76–84</sup> It should be noted that almost all of the studies were conducted in patients undergoing coronary angiography or PCI. A few included patients undergoing noncardiac angiography or angioplasty<sup>54–56,70</sup> but only 1 study has been conducted in patients receiving intravenous contrast medium.<sup>74</sup> Most trials have incorporated adequate intravenous volume expansion, typically with saline 0.45%.

A standard oral regimen of 600 mg twice daily for 24 hours the day before and the day of the procedure has been evaluated in many studies, compared with a placebo group or an untreated control group. However, a number of dif-

Table 4  
N-acetylcysteine (NAC) trials\*

| Study                           | Aim                               | Patients (N)                                       | Patient Type                           | Procedures   | NAC Dose  | Control  | Route of Administration | CIN Definition  | CIN Incidence |                  | p Value | Outcomes  | Conclusions   |
|---------------------------------|-----------------------------------|--|--|--|---|--|-------------------------|---|---------------|------------------|---------|---|---|
|                                 |                                   |  |  |  |   |  |                         |   | NAC           | Control          |         |   |   |
| Baker et al <sup>19</sup>       | RCT                               | 80: 41<br>NAC, 39<br>control                       | SCr >1.36 mg/dL or CrCl <50 mL/min     | Coronary angiography or PCI  | 150 mg/kg in 500 mL saline before and 50 mg/kg in 500 mL saline after procedure | Saline alone   | IV                      | ≥25% increase in SCr at 48 hr or 96 hr                                      | 4.90%         | 20.50%           | 0.045   | Change in mean SCr at 48 hr -0.08 mg/dL for NAC vs +0.05 for saline (p = 0.044)   | Significant benefit from NAC  |
| Agrawal et al <sup>50</sup>     | RCT (novel NAC dose strategy)     | 25: 11<br>NAC, 14<br>control                       | SCr ≥1.5 mg/dL or CrCl ≤50 mL/min      | Coronary angiography and/or PCI  | 800 mg 12 hr and 600 mg 2 hr before angiography; 600 mg 6 hr after angiography  | Placebo  | PO                      | ≤0.5 mg/dL increase in SCr or ≥25% increase at 48 hr                        | 18%           | 14%              | NS      | Change in mean SCr at 48 hr similar for both groups, 0.14 mg/dL NAC vs 0.06 mg/dL placebo (p = 0.6)                                       | Underpowered, so no firm conclusions can be drawn   |
| Allaqaband et al <sup>51</sup>  | RCT (NAC vs fenoldopam vs saline) | 123: 45<br>NAC, 38<br>fenoldopam,<br>40<br>control | SCr >1.6 mg/dL or CrCl <60 mL/min      | Cardiovascular procedures, including left heart catheterization with coronary angiography, coronary angiography with PCI | 600 mg NAC bid on day before and day of procedure                               | No drug  | PO                      | ≥0.5 mg/dL increase in SCr at 48 hr   | 17.70%        | 15.30%           | 0.919   | Change in mean SCr at 48 hr similar for all groups, 0.01 mg/dL NAC vs 0.09 saline (p = 0.701)   | No additional benefit over saline   |
| Azmus et al <sup>52</sup>       | RCT                               | 397: 196<br>NAC,<br>201<br>control                 | Cr ≥1.3 mg/dL, with DM or ≥70 yr       | Elective diagnostic and therapeutic cardiac procedures   | 600 mg bid on day before and day of procedure; 600 mg on day after procedure    | Placebo  | PO                      | ≥25% increase in SCr at 48 hr or ≥0.5 mg/dL increase to ≥1.3 mg/dL at 48 hr | 7.10%         | 8.40%            | 0.62    | Change in mean SCr at 48 hr similar for both groups, +0.076 mg/dL NAC vs +0.101 placebo (p = 0.33)  | Not effective in patients at risk receiving mainly HOCM   |
| Boccalandro et al <sup>53</sup> | Nonblinded, nonrandomized study   | 179: 73<br>NAC,<br>106<br>control                  | SCr >1.2 mg/dL or CrCl <50 mL/min      | Cardiac catheterization  | 600 mg bid on day before and day of procedure                                   | No drug  | PO                      | ≥0.5 mg/dL increase in SCr at 48 hr   | 13%           | 12%              | 0.84    | Change in mean SCr at 48 hr similar for both groups, +0.17 mg/dL NAC vs +0.19 mg/dL placebo (p = 0.77)                                    | No significant benefit from NAC   |
| Briguori et al <sup>54</sup>    | RCT                               | 183: 92<br>NAC, 91<br>control                      | SCr >1.2 mg/dL and/or CrCl <70 mL/min  | Coronary and/or peripheral angiography and/or angioplasty  | 600 mg bid on day before and day of procedure                                   | No drug  | PO                      | ≥25% increase in SCr at 48 hr   | 6.50%         | 11%              | 0.22    | In patients with low dose of CM (<140 mL), significantly lower incidence of CIN with NAC: 0% vs 8.5% for saline (p = 0.02)                | Significant benefit from NAC, only when a small volume of CM is used  |
| Briguori et al <sup>55</sup>    | RCT (NAC vs fenoldopam)           | 192: 97<br>NAC, 95<br>fenoldopam                   | SCr ≥1.5 mg/dL and/or CrCl <60 mL/min  | Coronary and/or peripheral angiography and/or angioplasty  | 1,200 mg bid on day before and day of procedure                                 | Fenoldopam 0.1 µg/kg/min 1 hr before and 12 hr after procedure | PO                      | ≥0.5 mg/dL increase in SCr at 48 hr   | 4.10%         | Fenoldopam 13.7% | 0.019   | Change in mean SCr at 48 hr similar for both groups, -0.12 mg/dL NAC vs -0.04 mg/dL fenoldopam (p = 0.77)                                 | NAC seems more effective than fenoldopam in preventing CIN  |
| Briguori et al <sup>56</sup>    | RCT, NAC SD vs NAC DD             | 223: 109<br>SD, 114<br>DD                          | SCr ≥1.5 mg/dL and/or CrCl < 60 mL/min | Coronary and/or peripheral procedures  | 1,200 mg NAC (DD) bid before and on day of procedure                            | 600 mg NAC (SD) bid before and after procedure                 | PO                      | ≥0.5 mg/dL increase in SCr at 48 hr   | 3.5% DD       | 11% SD           | 0.038   | Patients with high dose of contrast medium (≥140 mL), significantly higher incidence of CIN in SD group: 18.9% vs 5.4% for DD (p = 0.039) | DD of NAC can be more effective than the standard dose in preventing CIN, especially when a high volume of CM is used |

Table 4  
(continued)

|                                   |  |                                |  |   |   |         |    |   |   |  |       |  |  |
|-----------------------------------|--|--------------------------------|--|---|---|---------|----|---|---|--|-------|--|--|
| Diaz-Sandoval et al <sup>57</sup> | RCT  | 54: 25<br>NAC, 29<br>control   | SCr $\geq 1.4$ mg/dL<br>or CrCl $< 50$<br>mL/min                                     | Elective cardiac<br>catheterization         | 600 mg bid, 1 dose<br>before, 3 after<br>procedure                                    | Placebo | PO | $\geq 0.5$ mg/dL<br>increase in<br>SCr or $\geq 25\%$<br>increase at 48<br>hr                                   | 8%  | 45%  | 0.005 | At 48 hr change in<br>mean SCr was<br>$+0.32$ mg/dL for<br>placebo vs $-0.13$<br>for NAC<br>( $p < 0.0001$ )   | NAC reduces the risk<br>of CIN in patients<br>with chronic renal<br>insufficiency  |
| Drager et al <sup>58</sup>        | RCT  | 24: 13<br>NAC, 11<br>control   | SCr $> 1.4$ but<br>$< 5.0$ mg/dL<br>and CrCl $< 70$<br>mL/min/1.73<br>m <sup>2</sup> | Coronary<br>angiography                     | 600 mg bid for 4<br>periprocedure days<br>beginning 2 days<br>before the<br>procedure | Placebo | PO | NR  | NR  | NR   | NR    | Significant increase<br>in CrCl in NAC<br>patients ( $p =$<br>$0.02$ ); no change<br>in placebo group  | In chronic renal failure<br>patients, the<br>improvement in renal<br>function induced by<br>NAC is associated<br>with suppression of<br>oxidant<br>stress-induced<br>proximal tubule<br>injury                                     |
| Durham et al <sup>59</sup>        | RCT  | 79: 38<br>NAC, 41<br>control   | SCr $> 1.7$ mg/dL  | Coronary<br>angiography                     | 1,200 mg 1 hr before<br>and 3 hr after<br>procedure                                   | Placebo | PO | $\geq 0.5$ mg/dL<br>increase in<br>SCr at 48 hr   | 26.30%  | 22%  | NS    | —  | No significant benefit<br>from NAC   |
| Efrati et al <sup>60</sup>        | RCT  | 49: 24<br>NAC, 25<br>control   | SCr $> 1.2$ mg/dL  | Coronary<br>angiography                     | 1,000 mg bid 24 hr<br>before and 24 hr<br>after procedure                             | Placebo | PO | $\geq 25\%$ increase<br>in SCr at 24<br>hr or 96 hr   | 0%  | 8%   | NR    | Change in mean<br>CrCl at 24 hr: 5.3<br>mL/min increase<br>for NAC ( $p =$<br>$0.13$ ); 13.8 mL/<br>min decrease for<br>placebo<br>( $p < 0.0001$ )                              | NAC treatment has a<br>short- and relative<br>long-term<br>renoprotective effect   |
| Fung et al <sup>61</sup>          | Open-label trial   | 91: 46<br>NAC, 45<br>control   | SCr 1.69–4.52<br>mg/dL   | Coronary<br>angiography or<br>PCI           | 400 mg tid day<br>before and day of<br>procedure                                      | No drug | PO | $\geq 0.5$ mg/dL<br>increase in<br>SCr at 48 hr<br>or $\geq 25\%$<br>decrease in<br>GFR $\geq 25\%$<br>at 48 hr | 17.40%  | 13.30%   | 0.8   | No significant<br>difference<br>between groups<br>in change in SCr<br>( $p = 0.7$ ) or GFR<br>( $p = 0.7$ )  | No significant benefit<br>from NAC   |
| Gill et al <sup>62</sup>          | Retrospective<br>comparison<br>NAC vs<br>volume<br>expansion<br>alone; plus sex<br>as a CIN risk<br>factor | 146: 69<br>NAC, 77<br>control  | SCr $\geq 1.2$ mg/dL   | Cardiac or<br>peripheral<br>angiography     | 600 mg bid for 2<br>periprocedure days  | No drug | PO | $\geq 0.5$ mg/dL<br>increase in<br>SCr at 48 hr   | Men<br>5.26%,<br>women<br>16.12%,<br>overall<br>10.1% | Men 24%,<br>women<br>48.14%,<br>overall<br>32.5% | NR    | Change in mean<br>SCr at 48 hr,<br>NAC: men 0.15<br>mg/dL, women<br>0.14 mg/dL;<br>control: men 0.23<br>mg/dL, women<br>0.55 mg/dL   | No benefit from NAC<br>beyond that seen<br>with saline alone;<br>women were less<br>likely to receive<br>hydration, received<br>less protection from<br>saline alone; NAC<br>seemed to minimize<br>the difference<br>between sexes |
| Goldenberg et al <sup>63</sup>    | RCT  | 80: 41<br>NAC, 39<br>control   | SCr $\geq 1.5$ mg/dL<br>or CrCl $< 50$<br>mL/min                                     | Coronary<br>angiography                     | 600 mg tid for 48 hr<br>starting 24 hr<br>before procedure                            | Placebo | PO | $\geq 0.5$ mg/dL<br>increase in<br>SCr at 48 hr   | 10%   | 8%   | 0.52  | No significant<br>difference in<br>clinical events or<br>hospital stay   | No significant benefit<br>from NAC   |
| Kay et al <sup>64</sup>           | RCT  | 200: 102<br>NAC, 98<br>control | SCr $> 1.2$ mg/dL<br>or CrCl $< 60$<br>mL/min  | Coronary<br>angiography<br>with/without PCI | 600 mg bid on day<br>before and day of<br>procedure                                   | Placebo | PO | $\geq 25\%$ increase<br>in SCr at 48<br>hr  | 4%  | 12%  | 0.03  | In NAC group CrCl<br>was significantly<br>increased at 2<br>days ( $p < 0.001$ );<br>in placebo group,<br>increase in CrCl<br>at 2 days was not<br>significant<br>( $p = 0.15$ ) | NAC reduced CIN<br>incidence   |
| Kefer et al <sup>65</sup>         | RCT  | 108: 53<br>NAC, 51<br>control  | Normal renal<br>function or<br>mild or<br>moderate renal<br>failure                  | Coronary<br>angiography<br>and/or PCI       | 1,200 mg 12 hr<br>before procedure,<br>1,200 mg after<br>CM administration            | Placebo | IV | $\geq 0.5$ mg/dL<br>increase in<br>SCr or $\geq 25\%$<br>increase at 24<br>hr                                   | 3.80%   | 5.90%  | 0.98  | Mean SCr remained<br>unchanged at 24<br>hr in both groups  | No significant benefit<br>from NAC   |
| MacNeill et al <sup>66</sup>      | RCT  | 43: 21<br>NAC, 22<br>control   | SCr $\geq 1.5$ mg/dL   | Coronary<br>angiography                     | 5 doses 600 mg bid<br>starting day of<br>procedure                                    | Placebo | PO | $\geq 25\%$ increase<br>in SCr at 72<br>hr  | 4.76%   | 31.81%   | 0.046 | —  | NAC reduced CIN<br>incidence   |

Table 4  
(continued)

| Study                         | Aim   | Patients (N)   | Patient Type  | Procedures                                  | NAC Dose   | Control             | Route of Administration | CIN Definition  | CIN Incidence                                |  | p Value                                       | Outcomes  | Conclusions   |
|-------------------------------|---|--|---|---|--|---------------------|-------------------------|---|--|--|---|---|---|
|                               |   |  |   |   |  |                     |                         |   | NAC  | Control                                      |   |   |   |
| Miner et al <sup>67</sup>     | RCT   | 180: 95<br>NAC, 85<br>control                                    | SCr >2.2 mg/dL<br>or CrCl <50<br>mL/min                                     | Coronary<br>angiography or<br>PCI           | 1–2 doses (2,000<br>mg) before<br>procedure, 1 dose<br>postprocedure | Placebo             | PO                      | 25% increase in<br>SCr at 48–72<br>hr                                     | 9.60%  | 22.20%                                       | 0.04  | Long-term<br>composite end<br>point (death,<br>nonfatal MI,<br>dialysis or repeat<br>hospitalization<br>for cardiac causes<br>at mean 9.5 mo),<br>24.2% NAC vs<br>21.2% placebo | NAC reduced CIN, but<br>there was no<br>decrease in adverse<br>outcomes at 9 mo.<br>Patients with and<br>without CIN had<br>similar outcomes at<br>9 mo |
| Ochoa et al <sup>68</sup>     | RCT (abbreviated<br>NAC dosing)                                     | 80: 36<br>NAC, 44<br>control                                     | SCr >1.8 mg/dL<br>(men), >1.6<br>mg/dL<br>(women) or<br>CrCl <50 mL/<br>min | Coronary<br>angiography<br>and/or PCI       | 1,000 mg NAC 1 hr<br>before and 4 hr<br>after procedure              | Placebo             | PO                      | ≥0.5 mg/dL<br>increase in<br>SCr or ≥25%<br>increase at 48<br>hr          | 8%   | 25%  | 0.051   | Mean SCr increase<br>at 48 hr, 0.08<br>mg/dL for NAC,<br>0.17 mg/dL for<br>placebo. Study<br>terminated after<br>18 months<br>because of poor<br>recruitment                    | Abbreviated oral NAC<br>prevents increase in<br>SCr and may prevent<br>CIN. Large<br>randomized trial<br>needed to confirm<br>these findings            |
| Oldemeyer et al <sup>69</sup> | RCT   | 96: 49<br>NAC, 47<br>control                                     | SCr >1.2 mg/dL<br>and CrCl <50<br>mL/min                                    | Coronary<br>angiography                     | 1,500 mg bid for<br>2 days starting<br>evening before<br>procedure   | Placebo             | PO                      | ≥0.5 mg/dL<br>increase in<br>SCr or ≥25%<br>increase at 24<br>hr or 48 hr | 8.20%  | 6.40%  | 0.74  | Mean SCr changes<br>from baseline not<br>significantly<br>different between<br>groups   | NAC does not reduce<br>the risk for CIN   |
| Rashid et al <sup>70</sup>    | RCT   | 94: 46<br>NAC, 48<br>control                                     | Normal and<br>raised SCr  | Peripheral<br>angiography or<br>angioplasty | 1,000 mg before and<br>after procedure                               | Placebo             | IV                      | ≥0.5 mg/dL<br>increase in<br>SCr or ≥25%<br>increase at 48<br>hr          | Normal<br>SCr, 0;<br>raised<br>SCr,<br>17.6% | Normal<br>SCr, 0;<br>raised<br>SCr,<br>14.3% | Normal<br>SCr,<br>NS;<br>raised<br>SCr,<br>NS | No significant<br>difference in<br>mean change in<br>SCr or CrCl<br>between groups  | No benefit of NAC in<br>preventing CIN  |
| Raven et al <sup>71</sup>     | Retrospective<br>review of<br>medical<br>records: NAC<br>vs no drug | 60: 32<br>NAC, 28<br>control                                     | SCr >1.2 mg/dL  | Cardiac<br>catheterization                  | 600 mg bid day<br>before and day of<br>procedure                     | No drug             | PO                      | ≥0.5 mg/dL<br>increase in<br>SCr at 48–72<br>hr                           | 12.50%                                       | 25%  | 0.21  | Median increase in<br>SCr at 48–72 hr,<br>0 mg/dL for<br>NAC vs 0.25<br>mg/dL for<br>placebo (p =<br>0.001)   | NAC significantly<br>reduced SCr levels<br>after contrast media<br>administration   |
| Shyu et al <sup>72</sup>      | RCT   | 121: 60<br>NAC, 61<br>control                                    | Mean SCr 2.8<br>mg/dL   | Cardiac<br>angiography<br>and/or PCI        | 400 mg bid on the<br>day before and<br>day of procedure              | Placebo             | PO                      | ≥0.5 mg/dL<br>increase in<br>SCr at 48 hr                                 | 3.30%  | 24.60%                                       | <0.001  | Change in mean<br>SCr at 48 hr,<br>–0.29 mg/dL for<br>NAC vs +0.24<br>mg/dL for control<br>(p <0.001)   | NAC reduced the<br>incidence of CIN<br>after contrast media<br>administration   |
| Tadros et al <sup>73</sup>    | Comparison with<br>historical<br>controls                           | 55<br>consecutive<br>patients<br>vs 55<br>historical<br>controls | SCr >1.2 mg/dL<br>or CrCl <50<br>mL/min                                     | Coronary<br>angiography                     | 600 mg × 4 (3 doses<br>before, 1 after<br>procedure)                 | No drug             | PO                      | ≥0.5 mg/dL<br>increase in<br>SCr or ≥25%<br>increase at 24<br>or 48 hr    | 5.40%  | 16.4%<br>(historical<br>controls)            | 0.02  | Change in mean<br>SCr at 48 hr,<br>–0.4 mg/dL for<br>NAC vs +0.1<br>mg/dL for control<br>(p <0.001)   | NAC prevented the<br>reduction in renal<br>function after<br>contrast media<br>administration   |
| Tepel et al <sup>74</sup>     | RCT   | 83: 41<br>NAC, 42<br>control                                     | SCr >1.2 mg/dL<br>or CrCl <50<br>mL/min                                     | Computed<br>tomography                      | 600 mg bid day<br>before and day of<br>procedure                     | Placebo             | PO                      | ≥0.5 mg/dL<br>increase in<br>SCr at 48 hr                                 | 2%   | 21%  | 0.01  | Change in mean<br>SCr at 48 hr,<br>–0.4 mg/dL for<br>NAC vs +0.2<br>mg/dL for control<br>(p <0.001)   | NAC prevented the<br>reduction in renal<br>function in patients<br>with renal<br>insufficiency  |
| Webb et al <sup>75</sup>      | RCT   | 487: 242<br>NAC,<br>245<br>control                               | GFR <50 mL/<br>min  | Cardiac<br>catheterization or<br>PCI        | 500 mg immediately<br>before procedure                               | Placebo<br>(saline) | IV                      | >5 mL/min<br>decrease in<br>CrCl<br>(Cockcroft-<br>Gault<br>formula)      | 23.30%                                       | 20.70%                                       | 0.57  | Study terminated<br>early because of<br>futility  | IV NAC ineffective in<br>preventing CIN   |

CIN = contrast-induced nephropathy; CrCl = creatinine clearance; DD = double dose; GFR = glomerular filtration rate; IV = intravenous; NAC = N-acetylcysteine; NR = not reported; NS = not significant; PCI = percutaneous coronary intervention; PO = oral; RCT = randomized, controlled trial; SCr = serum creatinine; SD = single dose.

\* 1 mg/dL = 88.4 μmol/L.

Table 5  
Summary of published *N*-acetylcysteine (NAC) meta-analyses

| Study                          | No. of Trials Included | Patients (N) | Conclusions  |
|--------------------------------|------------------------|--------------|--|
| Pannu et al <sup>76</sup>      | 15                     | 1,776        | NAC may reduce CIN, but borderline significance and trials are heterogeneous                             |
| Alonso et al <sup>77</sup>     | 8                      | 885          | NAC reduces the risk for CIN   |
| Birck et al <sup>78</sup>      | 7                      | 805          | NAC significantly reduces the risk for CIN   |
| Guru and Fremes <sup>79</sup>  | 11                     | 1,203        | Suggests a protective effect of NAC against CIN  |
| Isenbarger et al <sup>80</sup> | 7                      | 805          | NAC significantly reduces the risk of CIN  |
| Bagshaw et al <sup>81</sup>    | 14                     | 1,261        | Heterogeneity between studies (possibly related to elective/emergency angiography); results inconsistent |
| Misra et al <sup>82</sup>      | 5                      | 643          | Oral NAC + saline is beneficial in patients with RI  |
| Kshirsagar et al <sup>83</sup> | 16                     | 1,538        | Heterogeneity between studies; results too inconclusive to warrant a conclusion                          |
| Nallamothe et al <sup>84</sup> | 20                     | 2,195        | NAC may reduce CIN but trials are inconsistent   |

CIN = contrast-induced nephropathy; RI = renal insufficiency.

ferent dosing regimens have also been evaluated. Briguori and colleagues<sup>56</sup> compared the standard oral dose (600 mg twice daily) with a double dose of NAC (1,200 mg twice daily). CIN, defined as an increase in the serum creatinine of  $\geq 0.5$  mg/dL ( $\geq 44.2$   $\mu$ mol/L) at 48 hours, occurred in 3.5% of the double-dose group, compared with 11% of the single-dose group ( $p = 0.038$ ). The difference was significant in patients receiving higher volumes of contrast medium but not in the subgroup receiving  $< 140$  mL of contrast medium.<sup>56</sup> A beneficial effect on creatinine clearance was observed with 1-g doses in patients with mild renal impairment undergoing coronary angiography.<sup>60</sup> However, in other studies, 1,200-mg and 1,500-mg doses were not effective.<sup>59,69</sup>

Because NAC initiation the day before contrast medium administration is possible only for planned procedures, various alternatives have been assessed that might be suitable for use in urgent cases. With an abbreviated oral dosing schedule (1,000 mg 1 hour before and 4 hours after the procedure), CIN occurred in 8% of patients in the NAC group and in 25% of patients in the placebo group ( $p = 0.051$ ).<sup>68</sup> In patients undergoing angiography for peripheral vascular disease, intravenous NAC (1,000 mg before and after the procedure) did not confer any benefit over saline alone.<sup>70</sup> However, a higher dose of

intravenous NAC (150 mg/kg in 500 mL saline over 30 minutes preprocedure and 50 mg/kg in 500 mL saline over 4 hours postprocedure) was associated with a significant reduction in the risk for CIN (5% vs 21%;  $p = 0.045$ ) in cardiology patients.<sup>19</sup> The largest NAC trial, in which NAC 500 mg was given intravenously immediately before the procedure, was terminated early after interim analysis because of failure to show benefit and a determination that trial continuation was unlikely to show benefit after the randomization of 487 patients. The primary end point, defined as a decrease in creatinine clearance from baseline of a  $\geq 5$  mL/min, occurred in 23.3% of patients in the NAC group and in 20.7% of patients in the placebo group ( $p = 0.57$ ).<sup>75</sup>

The published meta-analyses include different numbers of trials, between 5 and 20, depending on the inclusion criteria adopted and the date on which they were undertaken (Table 5).<sup>76–84</sup> Some included trials published only as abstracts and/or included unpublished trials, whereas others were confined to trials published in the peer-reviewed literature. All of the meta-analyses highlight the heterogeneity of NAC trials, which is generally unexplained and limits the conclusions that can be drawn. Some analyses include funnel plots and the Begg test, indicating that there may be a publication bias, with

smaller negative trials underrepresented.<sup>76,81</sup> Most of the authors highlight the need for more trials and/or further meta-analysis with patient-level data. The conclusions vary between statements that NAC is beneficial<sup>77–80,82</sup> and more cautious interpretations that more data are required.<sup>76,81,83,84</sup>

A recent study has suggested that the apparent benefit of NAC observed in some trials may be a consequence of an effect on serum creatinine levels that does not reflect a real improvement in GFR. In normal volunteers not receiving contrast medium, NAC treatment was associated with a decrease in serum creatinine levels and an increase in the eGFR calculated from the serum creatinine, but it had no effect on serum levels of cystatin C, a better marker of GFR. It is possible that NAC causes a decrease in serum creatinine through other mechanisms such as renal tubular secretion or increased muscle metabolism.<sup>85</sup>

**FENOLDOPAM/DOPAMINE.** The hypothesis that dopamine might reduce the risk for CIN by causing renal vasodilation and increasing renal blood flow led to its clinical evaluation (Table 6).<sup>30,86–91</sup> There were 3 small trials and 1 uncontrolled study that suggested that dopamine reduced the risk for CIN.<sup>86–89</sup> A small hemodynamic study suggested that the use of dopamine was associated with an increased risk for CIN in patients with diabetes mellitus but might be protective in patients without diabetes.<sup>90</sup>

However, a prospective, randomized, double-blind trial showed that low-dose dopamine (2  $\mu\text{g}/\text{kg}$  per min) in addition to intravenous saline 0.45% was no more effective than adequate volume expansion in reducing the risk for CIN in patients with mild or moderate renal impairment.<sup>91</sup> In patients with peripheral vascular disease, the increase in serum creatinine was greater in patients receiving dopamine, suggesting a deleterious effect in this subgroup.

Fenoldopam is a selective dopamine A<sub>1</sub> receptor agonist that might theoretically increase the blood flow to the renal medulla selectively. Several uncontrolled studies (historical controls, retrospective review) suggested that it was effective in reducing the risk for CIN,<sup>92–96</sup> and the results of a pilot trial were promising.<sup>17</sup> Trial results are summarized in Table 7.<sup>17,51,55,93–97</sup> There were 2 prospective randomized trials that showed negative results.<sup>51,97</sup> In the first trial, patients were randomized to saline alone or with fenoldopam (0.1  $\mu\text{g}/\text{kg}$  per min for 4 hours before and after the procedure); a third arm was treated with NAC. The incidence of CIN was similar in the fenoldopam (15.7%) and control (15.3%) groups and there was no benefit over saline alone.<sup>51</sup> A second larger trial also confirmed the lack of benefit with fenoldopam. In this double-blind trial, 315 patients, all with saline 0.45%, were randomized to fenoldopam (0.05  $\mu\text{g}/\text{kg}$  per min titrated to 0.1  $\mu\text{g}/\text{kg}$  per min) or placebo starting 1 hour before the procedure and continuing for 12 hours after-

ward. There was no significant difference in the incidence of CIN within 96 hours in the 2 groups (fenoldopam, 33.6%; placebo, 30.1%) or in the rates of dialysis, rehospitalization, or death at 30 days.<sup>97</sup>

**CALCIUM CHANNEL BLOCKERS.** Calcium channel blockers have been evaluated for reduction in the risk for CIN because of their vasodilatory properties. Various dihydropyridine calcium antagonists have been evaluated for CIN prophylaxis with no consistent evidence of benefit. Nifedipine,<sup>98–100</sup> nitrendipine,<sup>101–103</sup> felodipine,<sup>104</sup> and amlodipine<sup>105</sup> have all been tested in small studies in patients at risk for CIN. One hemodynamic study suggested that nifedipine protected against the reduction in renal plasma flow and GFR that occurred with high-osmolality contrast media.<sup>100</sup>

**ATRIAL NATRIURETIC PEPTIDE (ANP).** ANP has multiple effects on the kidney and has been shown to be beneficial in animal models of CIN.<sup>106</sup> One study showed no significant difference in the incidence of acute renal failure after contrast medium administration between patients receiving ANP (50  $\mu\text{g}$  bolus, followed by an infusion of 1  $\mu\text{g}/\text{min}$ ) or mannitol (15%, 100 mL/hr) for 2 hours before and during cardiac catheterization. Renal blood flow was maintained in both groups.<sup>106</sup> In a subsequent double-blind, placebo-controlled trial, the incidence of CIN was not reduced by ANP at any of 3 doses (0.01, 0.05, 0.1  $\mu\text{g}/\text{kg}$  per min for 30 minutes before and 30 minutes after the procedure) compared with placebo.<sup>107</sup> A small hemodynamic study suggested that the use of ANP and other vasodilator agents was associated with an increased risk for CIN in patients with diabetes but might be protective in nondiabetic individuals.<sup>90</sup>

**L-ARGININE.** Theoretically, L-arginine might be renoprotective because it is a substrate for nitric oxide synthesis. However, a single infusion of L-arginine (300 mg/kg) immediately before coronary angiography did not prevent a decrease in creatinine clearance at 48 hours in patients with mild-to-moderate renal failure included in a randomized, double-blind, placebo-controlled trial.<sup>108</sup>

**Negative results:** These are potentially detrimental agents.

**FUROSEMIDE.** In 1 trial, furosemide (80 mg infused immediately before the procedure) plus saline was less effective than saline 0.45% alone in preventing acute decreases in renal function after cardiac angiography.<sup>109</sup> An uncontrolled study suggested that an infusion of saline 0.45%, mannitol 12.5 g, sodium bicarbonate, and furosemide 200 mg (NSMF) was potentially beneficial.<sup>8</sup> A forced diuresis regime including intravenous crystalloid, mannitol, furosemide and low-dose dopamine had no effect on the overall incidence of CIN.<sup>18</sup>

In a small study of 18 patients, furosemide pretreatment (1.5 mg/kg) added to an intravenous fluid protocol was associated with significantly worse renal function than was intravenous fluid alone ( $p < 0.005$ ). Significant

Table 6  
Dopamine trials\*

| Study                        | Aim  | Patients (N)                      | Patient Type   | Procedures  | Dopamine Dose  | Control/<br>Placebo<br>Dose | Route of<br>Administration | CIN<br>Definition  | CIN Incidence  |  |  | Outcomes   | Conclusions  |
|------------------------------|--|-----------------------------------|--|---|--|-----------------------------|----------------------------|--|--|--|--|--|--|
|                              |  |                                   |  |   |  |                             |                            |  | Dopamine   | Control  | p Value  |  |  |
| Abizaid et al <sup>30</sup>  | RCT (dopamine vs aminophylline vs saline)    | 60: 20/group                      | SCr $\geq 1.5$ mg/dL   | PCI   | 2.5 $\mu\text{g}/\text{kg}/\text{min}$ , 2 hr before and 12 hr after procedure                                 | Saline                      | IV                         | $\geq 25\%$ increase in SCr <sup>†</sup>                   | 50%  | Saline 30%; aminophylline 35%                                    | NS   | Length of stay, peak SCr, change in SCr, time to peak SCr, dialysis: NS between the 3 groups   | Dopamine is not superior to saline alone   |
| Hans et al <sup>86</sup>     | RCT  | 55: 28 dopamine, 27 control       | SCr $\geq 1.4$ mg/dL   | Abdominal aortography and lower-extremity arteriography | 2.5 $\mu\text{g}/\text{kg}/\text{min}$ , starting 1 hr preprocedure for a total of 12 hr                       | Saline                      | IV                         | $\geq 0.5$ mg/dL increase in SCr at 24, 48, 72, and 96 hr  | 0% (24 hr), 7.1% (48 hr), 14.3% (72 hr), 17.9% (96 hr) | 25.9% (24 hr), 28.6% (48 hr), 27% (72 hr), 44.4% (96 hr)         | 0.002 (24 hr), 0.026 (48 hr), 0.048 (72 hr), 0.031 (96 hr) | SCr higher in control group at day 1 (p = 0.002), CrCl decrease in control group but not dopamine group  | Low-dose dopamine can prevent an increase in SCr 24 hr after arteriography, but this protective effect is not sustained over subsequent days   |
| Hans et al <sup>87</sup>     | RCT  | 60: 30 dopamine, 30 control       | SCr 1.3–3.5 mg/dL  | Abdominal and lower-extremity arteriography             | 2.5 $\mu\text{g}/\text{kg}/\text{min}$ , starting at beginning of procedure for 12 hr                          | Placebo                     | IV                         | —  | —  | —  | —  | Change in SCr: increase on days 1–3 in the control group (p < 0.03 on days 1 and 3), stable in the dopamine group. Change in CrCl: significant decrease in the control group on day 1 only (p = 0.001), stable in the dopamine group | Dopamine prophylaxis reduces the effects of CM on renal function   |
| Kapoor et al <sup>88</sup>   | RCT  | 40: 20 dopamine, 20 control       | Patients with DM; mean SCr 1.5 mg/dL   | Coronary angiography                                    | 5 $\mu\text{g}/\text{kg}/\text{min}$ , from 30 min before to 6–8 hr after procedure                            | No drug                     | IV                         | $\geq 25\%$ increase in SCr at 24 hr                       | 0%   | 50%  | NR   | Significant increase in SCr in control group but not dopamine group  | Dopamine in renal doses appears to be effective in preventing CIN  |
| Hall et al <sup>89</sup>     | Sequential treatment periods, not randomized | 222, 30 of whom received dopamine | Stratified by SCr: group 1, $\geq 2$ mg/dL, n = 24; group 2, 1.3–1.9 mg/dL, n = 60; group 3, $\leq 1.2$ mg/dL, n = 148 | Peripheral or visceral angiography                      | 3 $\mu\text{g}/\text{kg}/\text{min}$ (commencing the evening before procedure, and continuing to next morning) | 12.5 g 25% mannitol         | IV                         | $\geq 1$ mg/dL or $\geq 50\%$ increase in SCr <sup>†</sup> | 0%   | Overall CIN incidence: group 1, 62%; group 2, 10.4%; group 3, 2% | —  | No patients receiving dopamine experienced an elevation in SCr   | Renal-dose dopamine may be beneficial for reducing the incidence of CIN in high-risk patients  |
| Weisberg et al <sup>90</sup> | RCT  | 50, 15 of whom received dopamine  | SCr $\geq 1.8$ mg/dL (14 with DM, 16 without DM)   | Cardiac catheterization                                 | 2 $\mu\text{g}/\text{kg}/\text{min}$ (commencing at start of procedure for 2 hr)                               | Saline alone                | IV                         | $\geq 25\%$ increase in SCr at 48 hr                       | Patients with DM 83%; patients without DM 0%           | Patients with DM 43%; patients without DM 38%                    | —  | Baseline RBF: significantly lower in patients with DM (p < 0.05); these patients had the greatest increase in RBF with vasodilator/diuretic drugs  | Vasodilator/diuretic drugs (including dopamine) were effective in reducing the risk for CIN in patients without DM; the higher risk for CIN in patients with DM was related to exaggerated renovascular reactivity |
| Gare et al <sup>91</sup>     | RCT  | 66: 33 dopamine, 33 control       | CRF and/or DM (SCr > 1.47 mg/dL, but < 2.26 mg/dL)   | Coronary angiography                                    | 2 $\mu\text{g}/\text{kg}/\text{min}$ dopamine for 48 hr  | Saline alone                | IV                         | $\geq 40\%$ increase in SCr <sup>†</sup>                   | 12%  | 6%   | NR   | Change in SCr: NS between the 2 groups; small, but significant increase in both groups. Subgroup of patients with PVD: significant increase in SCr in dopamine group   | No advantage of dopamine over adequate IV fluid; dopamine should be avoided in PVD patients  |

CIN = contrast-induced nephropathy; CM = contrast medium; CrCl = creatinine clearance; CRF = chronic renal failure; DM = diabetes mellitus; IV = intravenous; NR = not reported; NS = not significant; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; RBF = renal blood flow; RCT = randomized, controlled trial; SCr = serum creatinine.

\* 1 mg/dL = 88.4  $\mu\text{mol/L}$ .

† SCr measurement time frame unspecified.

Table 7  
Fenoldopam trials\*

| Study                          | Aim  | Patients (N)                      | Patient Type                              | Procedures   | Fenoldopam Dose  | Placebo/ Control Dose                       | Route of Administration | CIN Definition  | CIN Incidence  |                                   | p Value                                      | Outcomes   | Conclusions   |
|--------------------------------|--|-----------------------------------|---|--|--|---|-------------------------|---|--|-----------------------------------|--|--|---|
|                                |  |                                   |   |  |  |   |                         |   | Fenoldopam   | Control                           |  |  |   |
| Tumlin et al <sup>17</sup>     | Pilot RCT  | 45: 23 fenoldopam, 22 control     | SCr 2–5 mg/dL                             | Coronary/peripheral angiography  | 0.1 µg/kg/min (1 hr before and 4 hr after procedure)           | Placebo                                     | IV                      | 0.5 mg/dL or 25% increase in SCr at 48 hr                           | Entire group 21%; DM subgroup 33%  | Entire group 41%; DM subgroup 64% | NS (entire group and DM subgroup)            | Peak SCr at 72 hr; significantly higher in the placebo group (3.55 vs 2.77 mg/dL, p <0.05). Change in RPF at 1 hr; 15.8% increase in the fenoldopam group vs 33.2% decrease in the placebo group (p <0.01) | Fenoldopam appears to be a promising prophylactic agent for CIN, but larger multicenter trials are needed to confirm this   |
| Allaqaband et al <sup>51</sup> | RCT (fenoldopam vs NAC vs saline)  | 123: 38 fenoldopam, 40 control    | SCr ≥1.6 mg/dL or CrCl ≤60 mL/min         | Cardiovascular procedures, including left heart catheterization with coronary angiography, coronary angiography with PCI | 0.1 µg/kg/min fenoldopam 4 hr before and 4 hr after procedure  | No drug                                     | IV                      | ≥0.5 mg/dL increase in SCr at 48 hr                                 | 15.70%   | 15.30%                            | 0.919  | Change in mean SCr at 48 hr similar for all groups, 0.01 mg/dL fenoldopam vs 0.09 saline (p = 0.701)   | No additional benefit over saline   |
| Briguori et al <sup>55</sup>   | RCT (NAC vs fenoldopam)  | 192: 95 fenoldopam, 97 NAC        | SCr ≥1.5 mg/dL and/or CrCl <60 mL/min     | Coronary and/or peripheral angiography and/or angioplasty  | 0.1 µg/kg/min fenoldopam 1 hr before and 12 hr after procedure | NAC 1,200 mg bid before and after procedure | IV                      | ≥0.5 mg/dL increase in SCr at 48 hr                                 | 13.70%   | NAC 4.1%                          | 0.019  | Change in mean SCr at 48 hr similar for both groups, -0.12 mg/dL NAC vs -0.04 mg/dL fenoldopam (p = 0.77)  | Fenoldopam seems less effective than NAC in preventing CIN  |
| Kini and Sharma <sup>93</sup>  | Nonrandomized study (historical controls)  | 110 vs 117 historical controls    | SCr >1.5 mg/dL and ≥1 risk factor for CIN | PCI  | 0.1 µg/kg/min (15–20 min before and 6 hr after procedure)      | No drug (historical controls)               | IV                      | >25% increase in SCr at 48–72 hr or absolute increase of >0.5 mg/dL | 4.5%   | Historical controls 19%           | 0.001  | Peak SCr: significant difference between the 2 groups (2.05 mg/dL in the fenoldopam group vs 3.32 mg/dL in the control group; p <0.01)   | Evidence suggests protective effect of fenoldopam, which is more pronounced in patients with DM with moderate renal failure   |
| Kini et al <sup>94</sup>       | Retrospective analysis of the incidence and predictors of CIN in high-risk patients receiving fenoldopam | 260 (143 with DM, 117 without DM) | SCr ≥1.5 mg/dL                            | PCI  | 0.1 µg/kg/min (15–20 min before and 6 hr after procedure)      | No control                                  | IV                      | >25% increase in SCr at 48–72 hr or absolute increase of >0.5 mg/dL | Entire group 3.8% or 3.0%, depending on definition; patients with DM 2.8%; patients without DM 5.1% (p = NS) | NA                                | NA   | Peak SCr: entire group 2.01 mg/dL; patients with DM 2.07 mg/dL; patients without DM 1.92 mg/dl (p = NS for all)  | Data suggest that fenoldopam is especially renoprotective in patients undergoing PCI, with SCr ≥2.0 mg/dL and with or without DM; previously established risk factors did not predict CIN |
| Kini et al <sup>95</sup>       | Retrospective analysis   | 150 vs 117 historical controls    | SCr ≥1.5 mg/dL                            | PCI  | 0.1 µg/kg/min (15–20 min before and 6 hr after procedure)      | No drug (historical controls)               | IV                      | >25% increase in SCr at 48–72 hr                                    | Entire group 4.7%; patients with DM 3.5%; patients without DM 6.1% (p = NS, vs DM and non-DM)                | Historical controls 19%           | <0.001 (entire group vs historical controls) | Peak SCr 2.05 mg/dL in the fenoldopam group vs 2.93 mg/dL in the control group. Patients requiring dialysis: 0 in the fenoldopam group vs 6 in the control group (p = 0.001)                               | Data suggest that fenoldopam can help reduce the incidence of CIN, especially in patients with DM   |

Table 7  
(continued)

| Study                       | Aim                    | Patients (N)                      | Patient Type                                | Procedures  | Fenoldopam Dose  | Placebo/Control Dose                                       | Route of Administration | CIN Incidence                    |                              | p Value                    | Outcomes   | Conclusions  |
|-----------------------------|------------------------|-----------------------------------|---|---|--|--|-------------------------|----------------------------------|------------------------------|----------------------------|--|--|
|                             |                        |                                   |   |   |  |  |                         | CIN Definition                   | Control                      |                            |  |  |
| Madyoon et al <sup>96</sup> | Retrospective analysis | 46 vs 50 historical controls      | SCR ≥1.7 mg/dL if no DM or ≥1.5 mg/dL if DM | Multiple procedures including coronary angiography (56%)                                  | 0.1 µg/kg/min started 2 hr before procedure, titrated to a maximum of 0.5 µg/kg/min and continued to ≥4 hr after procedure | Historical controls receiving saline/dopamine/mannitol/ANP | IV                      | ≥25% increase in SCR at 48 hr    | 38%                          | NR                         | Increase in SCR at 48 hr 16% for fenoldopam vs 118% for historical controls                                  | Fenoldopam was associated with a low incidence of CIN; RCTs required |
| Stone et al <sup>97</sup>   | RCT                    | 315 (157 fenoldopam, 158 placebo) | CrCl <60 mL/min                             | Cardiovascular procedures, including coronary angiography, PCI, and left ventriculography | 0.1 µg/kg/min 1 hr preprocedure and 12 hr postprocedure  | Placebo  | IV                      | ≥25% increase in SCR at 24–96 hr | 15.9% (48 hr), 30.1% (96 hr) | 0.45 (48 hr), 0.61 (96 hr) | No significant difference in 30-day mortality, dialysis rate, or rehospitalization for fenoldopam vs placebo | No significant benefit from fenoldopam                               |

ANP = atrial natriuretic peptide; CIN = contrast-induced nephropathy; CrCl = creatinine clearance; DM = diabetes mellitus; IV = intravenous; NA = not available; NAC = N-acetylcysteine; NR = not reported; NS = not significant; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RPF = renal plasma flow; SCR = serum creatinine.  
\* 1 mg/dL = 88.4 µmol/L.

weight loss was observed in the patients treated with furosemide, suggesting that the potentially deleterious effect of furosemide was the result of a negative fluid balance.<sup>110</sup>

**MANNITOL.** There were 2 studies, only 1 published in full, that suggested that mannitol had a protective effect against CIN<sup>111–113</sup>; another 2 studies concluded that it had no effect.<sup>89,114</sup> A small hemodynamic study suggested that the use of mannitol was associated with an increased risk for CIN in patients with diabetes but might be protective in patients without diabetes.<sup>90</sup> The study cited above suggested an infusion of NSMF was potentially beneficial.<sup>8</sup>

Two randomized prospective trials provide no evidence to support a benefit from mannitol in patients at risk for CIN. In 1 trial, mannitol 25 g (just before the procedure) plus saline was less effective than saline 0.45% alone in preventing acute decreases in renal function after cardiac angiography.<sup>109</sup> A forced diuresis regime including intravenous crystalloid, mannitol, furosemide, and low-dose dopamine had no effect on the overall incidence of CIN. The trial design allowed for the effects of mannitol to be evaluated independently and the results showed that mannitol provided no additive benefit.<sup>18</sup>

**DUAL ENDOTHELIN RECEPTOR ANTAGONIST.** A non-selective dual endothelin A and B receptor antagonist was shown to have a detrimental effect and to exacerbate CIN.<sup>115</sup> The incidence of CIN was 56% in the patients receiving the endothelin receptor antagonist compared with 29% in the control group (p = 0.002).

**Withdrawal of Nephrotoxic Drugs**

The CIN Consensus Working Panel agreed that potentially nephrotoxic drugs should be withdrawn ≥24 hours before contrast administration in patients at risk for CIN (defined as an eGFR <60 mL/min).

**Withdrawal of Metformin**

Although not relevant to CIN prevention, acute renal failure increases the risk of lactic acidosis as a complication of metformin treatment. Hence, it is common practice to withdraw metformin before contrast administration to avoid the risk that metabolic acidosis might be precipitated if a postprocedure decline in renal function occurs. The CIN Consensus Working Panel agreed that metformin should be stopped at the time of the investigation or procedure and resumed 48 hours afterward, provided renal function remains within the normal range. If the patient’s baseline renal function is abnormal, metformin should be stopped 48 hours before the study and should only be restarted 48 hours afterward if renal

function is unchanged. In emergency situations, clinical judgment should be used and the patient should be monitored closely, with particular attention to hydration. This is in line with the recommendations of the European Society for Urogenital Radiology (ESUR)<sup>116</sup> and the Society for Cardiac Angiography and Interventions (SCAI).<sup>117</sup>

## Conclusion

The CIN Consensus Working Panel agreed that intravenous volume expansion reduces the risk for CIN and that patients should receive adequate intravenous volume expansion with isotonic crystalloid 1.0–1.5 mL/kg per hr for 3–12 hours before the procedure and for 6–24 hours afterward. The CIN Consensus Working Panel considered all the evidence and agreed that no adjunctive pharmacologic treatment has been proved conclusively to reduce the risk for CIN. They also agreed that hemodialysis is ineffective and that hemofiltration requires further validation. However, the CIN Consensus Working Panel agreed that in patients at increased risk for CIN (ie, with an eGFR <60 mL/min per 1.73 m<sup>2</sup>) consideration could be given to prophylactic treatment with any of the agents that have given promising results, specifically theophylline, statins, ascorbic acid, or PGE<sub>1</sub>. These agents deserve further evaluation. Nephrotoxic drugs should be withdrawn 24 hours before the procedure in patients at risk for CIN.

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