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_1 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 Nephrotoxic drugs should be withdrawn before contrast administration in patients at risk for CIN. **(Am J Cardiol 2006;98[suppl]:59K–77K)**

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.[1–5] 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.[6,7] 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.[8] 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.[9] 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.[10])

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).[9,11–15] The trial by Mueller and colleagues[9] 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 ≥0.5 mg/dL [44.2 μmol/L] within 48 hours) was significantly lower with saline 0.9% than with saline 0.45% (0.7% vs 2%; $p = 0.04$).[9] 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 ≥25% in serum creatinine within 48 hours) was significantly lower in the group receiving bicarbonate (1.7% vs 13.6%, $p = 0.02$).[11] 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 (≥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.[12] Another randomized trial also showed a trend toward a lower incidence of CIN with overnight intravenous fluid compared with bolus administration.[13]

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).[14] 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.[15] 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.[9,11–15] 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 (Group 1/Group 2)	Group 1		Group 2		CIN Definition	CIN Incidence		p Value
			Preprocedure Regime	Postprocedure Regime	Preprocedure Regime	Postprocedure Regime		Group 1	Group 2	
Mueller et al[9]	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[11]	$NaHCO_3$ vs NaCl infusion	60/59	$NaHCO_3$ 154-mEq/L infusion at 3 mL/kg IV for 1 hr	$NaHCO_3$ 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[12]	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[13]	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[14]	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[15]	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[16] 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[17] 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,[18] 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,[6,13] and a 5% incidence of pulmonary edema was reported in 1 study with *N*-acetylcysteine (NAC).[19] 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.[20–23] However, randomized trials of prophylactic hemodialysis showed that it is not effective in reducing the risk for CIN,[24,25] even when carried out within 1 hour[26] or simultaneously with contrast administration.[27] In a study of 17 patients with advanced chronic kidney disease, Frank and coworkers[27] 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.[28]

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 μmol/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 inhospital 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.[29] 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).

Table 2
Pharmacologic agents evaluated for contrast-induced nephropathy risk reduction

- Positive results (potentially beneficial)
  - —Theophylline/aminophylline
  - —Statins
  - —Ascorbic acid
  - —Prostaglandin E_1
- 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

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).[30–40] Of the 11 studies, 9 were randomized controlled trials (8 with theophylline, 1 with aminophylline) [30–38] and 2 were case-control studies (1 with aminophylline).[39,40] There appears to be some overlap between patients included in 2 of the reports.[34,35] 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,[34–36] another 3 studies showed no reduction.[30,32,33] Although CIN was not an end point in the other 3 trials, less decline in renal function was observed in patients receiving theophylline.[31,37,38] 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.[41] 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 index and potential for serious adverse effects including gastrointestinal, neurological, and cardiovascular effects.[42]

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[43] because they have beneficial effects on endothelial function, maintain nitric oxide production, and reduce oxidative stress.[44] A retrospective review of 1,002 patients with renal impairment (baseline serum creatinine ≥1.5 mg/dL [≥132.6 μmol/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 ($p = 0.028$).[43] The results of a large PCI registry study published since the literature search for this review also support this conclusion,[45] 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 ≥0.5 mg/dL (≥44.2 μmol/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 ($p = 0.03$).[45] 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/ Aminophylline Dose	Placebo/Control Dose	Route of Administration	CIN Definition	CIN Incidence		p Value	Outcomes	Conclusions
									Theophylline/ Aminophylline	Control			
Abizaid et al[30]	RCT (aminophylline vs dopamine vs saline)	60: 20/group	SCr ≥1.5 mg/dL	PCI	Aminophylline 4 mg/kg followed by 0.4 mg/kg/hr, 2 hr before and 12 hr after procedure	Saline	IV	≥25% increase in SCr†	35%	Saline 30%	NS	Length of stay, peak SCr, change in SCr, time to peak SCr, dialysis: NS between the 3 groups	Aminophylline is not superior to saline alone
Erley et al[31]	RCT	39: 19 theophylline, 20 control	Mean SCr 1.2 mg/dL; 43% with GFR <75 mL/min/1.72 m^2	CT or digital subtraction angiography	Theophylline 5 mg/kg, 45 min preprocedure	Placebo (saline)	IV	—	—	—	—	Change in GFR: significant decline in the placebo group from 88 to 75 mL/min ($p < 0.01$), but not the theophylline group	Theophylline can prevent CM-induced decrease in GFR in patients with/without RI
Erley et al[32]	RCT	80: 64 completed protocol (35 theophylline, 29 control)	SCr >1.5 mg/dL	CT or digital subtraction angiography	Theophylline 810 mg/day (270 mg in the morning, 540 mg in the evening), 2 days before and 3 days after procedure	Placebo	PO	0.5 mg/dL increase in SCr†	5.70%	3.40%	NS	Change in SCr, change in CrCl: NS in both groups; NAG excretion: increase in both groups, but significant ($p < 0.05$) in the placebo group only, on days 2 and 3	Oral/IV fluid preserved renal function, with no further benefit from theophylline
Gandhi et al[33]	RCT	21: 13 theophylline, 8 control	CrCl 86.9 mL/min, placebo; 89.7 mL/min theophylline	Coronary angiography	Theophylline 125 mg tid, 24 hr before and 48 hr after procedure	Placebo	PO	Significant renal impairment (not specified)	15%	12.50%	NS	Change in CrCl: NS in both groups (stable, compared with baseline, in both groups)	No evidence of protective effect of theophylline with this dose (125 mg tid) in a small group of patients
Huber et al[34]	RCT	100: 50 theophylline, 50 control	SCr ≥1.3 mg/dL	Various, 54 coronary angiography, 24 CT, 12 iliofemoral arteriography	Theophylline 200 mg, 30 min preprocedure	Placebo (saline)	IV	≥0.5 mg/dL increase in SCr at 48 hr	4%	16%	0.046	Change in SCr at 24 hr: theophylline, NS decrease from 2.07 to 1.97 mg/dL ($p = 0.99$); placebo, significant increase from 1.92 to 2.01 mg/dL ($p = 0.006$)	Prophylactic administration of 200 mg theophylline reduces the incidence of CIN in patients with RI
Huber et al[35]	RCT	100: 50 theophylline, 50 control	SCr ≥1.3 mg/dL	Coronary angiography	Theophylline 200 mg, 30 min preprocedure	Placebo (saline)	IV	≥0.5 mg/dL increase in SCr at 48 hr	4%	20%	0.0138	Change in SCr at 48 hr: theophylline, stable (1.65 mg/dL NS); placebo, significant increase over baseline (from 1.72 to 1.9 mg/dL, $p = 0.0007$)	Prophylactic administration of 200 mg theophylline reduces the incidence of CIN in patients with RI
Kapoor et al[36]	RCT	70: 35 theophylline, 35 control	Diabetes mellitus and SCr <3.0 mg/dL; mean GFR: control 85.4 mL/min, theophylline 86.8 mL/min	Coronary angiography	Theophylline 200 mg bid, for 24 hr before and 48 hr after procedure	No drug	PO	≥25% increase in SCr or ≥25% decrease in GFR†	SCr 0%; GFR 3%	SCr 20%; GFR 31%	0.017 (SCr); 0.004 (GFR)	Change in SCr: control group, increase from 1.19 to 1.44 mg/dL ($p = 0.03$); theophylline group, NS. Change in GFR: control group, decrease from 85.4 to 66.8 mL/min ($p = 0.008$); theophylline group, NS	Prophylactic administration of 200 mg bid theophylline reduces the incidence of CIN in patients with diabetes
Katholi et al[37]	RCT	93: 47 theophylline, 46 control	SCr <2.0 mg/dL	Coronary angiography/ left ventriculography	Theophylline 2.88 mg/kg, every 12 hr × 4; first dose at ≥1 hr preprocedure	Placebo	PO	—	—	—	—	Change in CrCl at 24 hr: significant decrease in the placebo-iopamidol group (18%, from 82 to 68 mL/min, $p < 0.05$), but not in the theophylline-iopamidol group; significant decrease in the placebo-diatrizoate group (42%, from 79 to 46 mL/min, $p < 0.01$) and in the theophylline-diatrizoate group (24%, from 80 to 61 mL/min, $p < 0.05$)	Supports the hypothesis that intrarenal adenosine is implicated in the pathogenesis of CIN

Table 3
(continued)

Kolonko et al[38]	RCT	58: 26 theophylline, 32 control	SCr <1.4 mg/dL; CrCl 107.5 mL/min (placebo), 106.4 mL/min (theophylline)	Radiologic examinations	Theophylline 165 mg, 30 min preprocedure	Placebo (saline)	IV	—	—	—	—	Change in GFR: reduction in placebo patients, from 107.5 to 85.4 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	Theophylline (165 mg) prevented RCA-induced impairment of renal excretion, endocrine and tubular function. Adenosine may play a role in pathogenesis of CIN
Huber et al[39]	Comparison with historical series at comparable risk of CIN	78	ICU patients with ≥1 risk factor for CIN	Radiographic procedures including CT	Theophylline 200 mg/70 kg (2.86 mg/kg), 30 min preprocedure	NA	IV	≥0.5 mg/dL increase in SCr at 48 hr	2%	Published historical controls 14%	<0.0001 (cases vs control series)	Change in SCr at 24 and 48 hr; not increased vs baseline, despite the large number of risk factors	Prophylactic administration of theophylline (200 mg/70 kg) markedly reduces the incidence of CIN in high-risk patients
Shammas et al[40]	Case-control study	26 aminophylline; 26 matched controls	SCr ≥1.4 mg/dL	Coronary and peripheral angiographic procedures	Aminophylline 200 mg, immediately before procedure	NA	IV	≥25% increase in SCr[†]	Cases 11.5%	Matched controls 11.5%	NS (cases vs matched controls)	Change in SCr: NS in both groups	Aminophylline does not protect against CIN

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.[46]

PROSTAGLANDIN E_1 (PGE_1). Because renal vasoconstriction is believed to contribute to the pathogenesis of CIN, preliminary studies have been undertaken with vasodilator prostaglandins. Misoprostol (a PGE_1 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.[47] A pilot study with intravenous PGE_1 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_1 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_1 groups compared with placebo, with the difference being significant at the 20-ng/kg per min dose ($p = 0.01$).[48,49] There were no clinically relevant changes in calculated creatinine clearance in any group.[48] 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).[19,50–75] Additionally, 9 published meta-analyses were identified, all documenting the significant heterogeneity between studies.[76–84] 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[54–56,70] but only 1 study has been conducted in patients receiving intravenous contrast medium.[74] 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[19]	RCT	80: 41 NAC, 39 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[50]	RCT (novel NAC dose strategy)	25: 11 NAC, 14 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[51]	RCT (NAC vs fenoldopam vs saline)	123: 45 NAC, 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	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[52]	RCT	397: 196 NAC, 201 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[53]	Nonblinded, nonrandomized study	179: 73 NAC, 106 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[54]	RCT	183: 92 NAC, 91 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[55]	RCT (NAC vs fenoldopam)	192: 97 NAC, 95 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[56]	RCT, NAC SD vs NAC DD	223: 109 SD, 114 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[57]	RCT	54: 25 NAC, 29 control	SCr ≥1.4 mg/dL or CrCl <50 mL/min	Elective cardiac catheterization	600 mg bid, 1 dose before, 3 after procedure	Placebo	PO	≥0.5 mg/dL increase in SCr or ≥25% increase at 48 hr	8%	45%	0.005	At 48 hr change in mean SCr was +0.32 mg/dL for placebo vs −0.13 for NAC (p <0.0001)	NAC reduces the risk of CIN in patients with chronic renal insufficiency
Drager et al[58]	RCT	24: 13 NAC, 11 control	SCr >1.4 but <5.0 mg/dL and CrCl <70 mL/min/1.73 m^2	Coronary angiography	600 mg bid for 4 periprocedure days beginning 2 days before the procedure	Placebo	PO	NR	NR	NR	NR	Significant increase in CrCl in NAC patients (p = 0.02); no change in placebo group	In chronic renal failure patients, the improvement in renal function induced by NAC is associated with suppression of oxidant stress–induced proximal tubule injury
Durham et al[59]	RCT	79: 38 NAC, 41 control	SCr >1.7 mg/dL	Coronary angiography	1,200 mg 1 hr before and 3 hr after procedure	Placebo	PO	≥0.5 mg/dL increase in SCr at 48 hr	26.30%	22%	NS	—	No significant benefit from NAC
Efrati et al[60]	RCT	49: 24 NAC, 25 control	SCr >1.2 mg/dL	Coronary angiography	1,000 mg bid 24 hr before and 24 hr after procedure	Placebo	PO	≥25% increase in SCr at 24 hr or 96 hr	0%	8%	NR	Change in mean CrCl at 24 hr: 5.3 mL/min increase for NAC (p = 0.13); 13.8 mL/min decrease for placebo (p <0.0001)	NAC treatment has a short- and relative long-term renoprotective effect
Fung et al[61]	Open-label trial	91: 46 NAC, 45 control	SCr 1.69–4.52 mg/dL	Coronary angiography or PCI	400 mg tid day before and day of procedure	No drug	PO	≥0.5 mg/dL increase in SCr at 48 hr or ≥25% decrease in GFR ≥25% at 48 hr	17.40%	13.30%	0.8	No significant difference between groups in change in SCr (p = 0.7) or GFR (p = 0.7)	No significant benefit from NAC
Gill et al[62]	Retrospective comparison NAC vs volume expansion alone; plus sex as a CIN risk factor	146: 69 NAC, 77 control	SCr ≥1.2 mg/dL	Cardiac or peripheral angiography	600 mg bid for 2 periprocedure days	No drug	PO	≥0.5 mg/dL increase in SCr at 48 hr	Men 5.26%, women 16.12%, overall 10.1%	Men 24%, women 48.14%, overall 32.5%	NR	Change in mean SCr at 48 hr, NAC: men 0.15 mg/dL, women 0.14 mg/dL; control: men 0.23 mg/dL, women 0.55 mg/dL	No benefit from NAC beyond that seen with saline alone; women were less likely to receive hydration, received less protection from saline alone; NAC seemed to minimize the difference between sexes
Goldenberg et al[63]	RCT	80: 41 NAC, 39 control	SCr ≥1.5 mg/dL or CrCl <50 mL/min	Coronary angiography	600 mg tid for 48 hr starting 24 hr before procedure	Placebo	PO	≥0.5 mg/dL increase in SCr at 48 hr	10%	8%	0.52	No significant difference in clinical events or hospital stay	No significant benefit from NAC
Kay et al[64]	RCT	200: 102 NAC, 98 control	SCr >1.2 mg/dL or CrCl <60 mL/min	Coronary angiography with/without PCI	600 mg bid on day before and day of procedure	Placebo	PO	≥25% increase in SCr at 48 hr	4%	12%	0.03	In NAC group CrCl was significantly increased at 2 days (p <0.001); in placebo group, increase in CrCl at 2 days was not significant (p = 0.15)	NAC reduced CIN incidence
Kefer et al[65]	RCT	108: 53 NAC, 51 control	Normal renal function or mild or moderate renal failure	Coronary angiography and/or PCI	1,200 mg 12 hr before procedure, 1,200 mg after CM administration	Placebo	IV	≥0.5 mg/dL increase in SCr or ≥25% increase at 24 hr	3.80%	5.90%	0.98	Mean SCr remained unchanged at 24 hr in both groups	No significant benefit from NAC
MacNeill et al[66]	RCT	43: 21 NAC, 22 control	SCr ≥1.5 mg/dL	Coronary angiography	5 doses 600 mg bid starting day of procedure	Placebo	PO	≥25% increase in SCr at 72 hr	4.76%	31.81%	0.046	—	NAC reduced CIN 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[67]	RCT	180: 95 NAC, 85 control	SCr >2.2 mg/dL or CrCl <50 mL/min	Coronary angiography or PCI	1–2 doses (2,000 mg) before procedure, 1 dose postprocedure	Placebo	PO	25% increase in SCr at 48–72 hr	9.60%	22.20%	0.04	Long-term composite end point (death, nonfatal MI, dialysis or repeat hospitalization for cardiac causes at mean 9.5 mo), 24.2% NAC vs 21.2% placebo	NAC reduced CIN, but there was no decrease in adverse outcomes at 9 mo. Patients with and without CIN had similar outcomes at 9 mo
Ochoa et al[68]	RCT (abbreviated NAC dosing)	80: 36 NAC, 44 control	SCr >1.8 mg/dL (men), >1.6 mg/dL (women) or CrCl <50 mL/min	Coronary angiography and/or PCI	1,000 mg NAC 1 hr before and 4 hr after procedure	Placebo	PO	≥0.5 mg/dL increase in SCr or ≥25% increase at 48 hr	8%	25%	0.051	Mean SCr increase at 48 hr, 0.08 mg/dL for NAC, 0.17 mg/dL for placebo. Study terminated after 18 months because of poor recruitment	Abbreviated oral NAC prevents increase in SCr and may prevent CIN. Large randomized trial needed to confirm these findings
Oldemeyer et al[69]	RCT	96: 49 NAC, 47 control	SCr >1.2 mg/dL and CrCl <50 mL/min	Coronary angiography	1,500 mg bid for 2 days starting evening before procedure	Placebo	PO	≥0.5 mg/dL increase in SCr or ≥25% increase at 24 hr or 48 hr	8.20%	6.40%	0.74	Mean SCr changes from baseline not significantly different between groups	NAC does not reduce the risk for CIN
Rashid et al[70]	RCT	94: 46 NAC, 48 control	Normal and raised SCr	Peripheral angiography or angioplasty	1,000 mg before and after procedure	Placebo	IV	≥0.5 mg/dL increase in SCr or ≥25% increase at 48 hr	Normal SCr, 0; raised SCr, 17.6%	Normal SCr, 0; raised SCr, 14.3%	Normal SCr, NS; raised SCr, NS	No significant difference in mean change in SCr or CrCl between groups	No benefit of NAC in preventing CIN
Raven et al[71]	Retrospective review of medical records: NAC vs no drug	60: 32 NAC, 28 control	SCr >1.2 mg/dL	Cardiac catheterization	600 mg bid day before and day of procedure	No drug	PO	≥0.5 mg/dL increase in SCr at 48–72 hr	12.50%	25%	0.21	Median increase in SCr at 48–72 hr, 0 mg/dL for NAC vs 0.25 mg/dL for placebo (p = 0.001)	NAC significantly reduced SCr levels after contrast media administration
Shyu et al[72]	RCT	121: 60 NAC, 61 control	Mean SCr 2.8 mg/dL	Cardiac angiography and/or PCI	400 mg bid on the day before and day of procedure	Placebo	PO	≥0.5 mg/dL increase in SCr at 48 hr	3.30%	24.60%	<0.001	Change in mean SCr at 48 hr, −0.29 mg/dL for NAC vs +0.24 mg/dL for control (p <0.001)	NAC reduced the incidence of CIN after contrast media administration
Tadros et al[73]	Comparison with historical controls	55 consecutive patients vs 55 historical controls	SCr >1.2 mg/dL or CrCl <50 mL/min	Coronary angiography	600 mg × 4 (3 doses before, 1 after procedure)	No drug	PO	≥0.5 mg/dL increase in SCr or ≥25% increase at 24 or 48 hr	5.40%	16.4% (historical controls)	0.02	Change in mean SCr at 48 hr, −0.4 mg/dL for NAC vs +0.1 mg/dL for control (p <0.001)	NAC prevented the reduction in renal function after contrast media administration
Tepel et al[74]	RCT	83: 41 NAC, 42 control	SCr >1.2 mg/dL or CrCl <50 mL/min	Computed tomography	600 mg bid day before and day of procedure	Placebo	PO	≥0.5 mg/dL increase in SCr at 48 hr	2%	21%	0.01	Change in mean SCr at 48 hr, −0.4 mg/dL for NAC vs +0.2 mg/dL for control (p <0.001)	NAC prevented the reduction in renal function in patients with renal insufficiency
Webb et al[75]	RCT	487: 242 NAC, 245 control	GFR <50 mL/min	Cardiac catheterization or PCI	500 mg immediately before procedure	Placebo (saline)	IV	>5 mL/min decrease in CrCl (Cockcroft-Gault formula)	23.30%	20.70%	0.57	Study terminated early because of futility	IV NAC ineffective in 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[76]	15	1,776	NAC may reduce CIN, but borderline significance and trials are heterogeneous
Alonso et al[77]	8	885	NAC reduces the risk for CIN
Birck et al[78]	7	805	NAC significantly reduces the risk for CIN
Guru and Fremes[79]	11	1,203	Suggests a protective effect of NAC against CIN
Isenbarger et al[80]	7	805	NAC significantly reduces the risk of CIN
Bagshaw et al[81]	14	1,261	Heterogeneity between studies (possibly related to elective/emergency angiography); results inconsistent
Misra et al[82]	5	643	Oral NAC + saline is beneficial in patients with RI
Kshirsagar et al[83]	16	1,538	Heterogeneity between studies; results too inconclusive to warrant a conclusion
Nallamothu et al[84]	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[56] 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 ≥0.5 mg/dL (≥44.2 μmol/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.[56] A beneficial effect on creatinine clearance was observed with 1-g doses in patients with mild renal impairment undergoing coronary angiography.[60] However, in other studies, 1,200-mg and 1,500-mg doses were not effective.[59,69]

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 ($p = 0.051$).[68] 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.[70] 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.[19] 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 ≥5 mL/min, occurred in 23.3% of patients in the NAC group and in 20.7% of patients in the placebo group ($p = 0.57$).[75]

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).[76–84] 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.[76,81] 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[77–80,82] and more cautious interpretations that more data are required.[76,81,83,84]

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.[85]

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).[30,86–91] There were 3 small trials and 1 uncontrolled study that suggested that dopamine reduced the risk for CIN.[86–89] 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.[90]

However, a prospective, randomized, double-blind trial showed that low-dose dopamine (2 μg/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.[91] 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_1 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,[92–96] and the results of a pilot trial were promising.[17] Trial results are summarized in Table 7.[17,51,55,93–97] There were 2 prospective randomized trials that showed negative results.[51,97] In the first trial, patients were randomized to saline alone or with fenoldopam (0.1 μg/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.[51] 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 μg/kg per min titrated to 0.1 μg/kg per min) or placebo starting 1 hour before the procedure and continuing for 12 hours afterward. 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.[97]

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,[98–100] nitrendipine,[101–103] felodipine,[104] and amlodipine[105] 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.[100]

ATRIAL NATRIURETIC PEPTIDE (ANP). ANP has multiple effects on the kidney and has been shown to be beneficial in animal models of CIN.[106] One study showed no significant difference in the incidence of acute renal failure after contrast medium administration between patients receiving ANP (50 μg bolus, followed by an infusion of 1 μg/min) or mannitol (15%, 100 mL/hr) for 2 hours before and during cardiac catheterization. Renal blood flow was maintained in both groups.[106] 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 μg/kg per min for 30 minutes before and 30 minutes after the procedure) compared with placebo.[107] 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.[90]

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.[108]

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.[109] 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.[8] A forced diuresis regime including intravenous crystalloid, mannitol, furosemide and low-dose dopamine had no effect on the overall incidence of CIN.[18]

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/ Placebo Dose	Route of Administration	CIN Definition	CIN Incidence		p Value	Outcomes	Conclusions
									Dopamine	Control			
Abizaid et al[30]	RCT (dopamine vs aminophylline vs saline)	60: 20/group	SCr ≥1.5 mg/dL	PCI	2.5 μg/kg/min, 2 hr before and 12 hr after procedure	Saline	IV	≥25% increase in SCr†	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[86]	RCT	55: 28 dopamine, 27 control	SCr ≥1.4 mg/dL	Abdominal aortography and lower-extremity arteriography	2.5 μg/kg/min, starting 1 hr preprocedure for a total of 12 hr	Saline	IV	≥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[87]	RCT	60: 30 dopamine, 30 control	SCr 1.3–3.5 mg/dL	Abdominal and lower-extremity arteriography	2.5 μg/kg/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[88]	RCT	40: 20 dopamine, 20 control	Patients with DM; mean SCr 1.5 mg/dL	Coronary angiography	5 μg/kg/min, from 30 min before to 6–8 hr after procedure	No drug	IV	≥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[89]	Sequential treatment periods, not randomized	222, 30 of whom received dopamine	Stratified by SCr: group 1, ≥2 mg/dL, n = 24; group 2, 1.3–1.9 mg/dL, n = 60; group 3, ≤1.2 mg/dL, n = 148	Peripheral or visceral angiography	3 μg/kg/min (commencing the evening before procedure, and continuing to next morning)	12.5 g 25% mannitol	IV	≥1 mg/dL or ≥50% increase in SCr†	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[90]	RCT	50, 15 of whom received dopamine	SCr ≥1.8 mg/dL (14 with DM, 16 without DM)	Cardiac catheterization	2 μg/kg/min (commencing at start of procedure for 2 hr)	Saline alone	IV	≥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[91]	RCT	66: 33 dopamine, 33 control	CRF and/or DM (SCr >1.47 mg/dL, but <2.26 mg/dL)	Coronary angiography	2 μg/kg/min dopamine for 48 hr	Saline alone	IV	≥40% increase in SCr†	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 μmol/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[17]	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[51]	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[55]	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[93]	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[94]	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[95]	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 Definition	CIN Incidence		p Value	Outcomes	Conclusions
									Fenoldopam	Control			
Madyoon et al[96]	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	13%	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[97]	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	19.9% (48 hr), 33.6% (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.[110]

MANNITOL. There were 2 studies, only 1 published in full, that suggested that mannitol had a protective effect against CIN[111–113]; another 2 studies concluded that it had no effect.[89,114] 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.[90] The study cited above suggested an infusion of NSMF was potentially beneficial.[8]

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.[109] 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.[18]

DUAL ENDOTHELIN RECEPTOR ANTAGONIST. A nonselective dual endothelin A and B receptor antagonist was shown to have a detrimental effect and to exacerbate CIN.[115] 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)[116] and the Society for Cardiac Angiography and Interventions (SCAI).[117]

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^2) consideration could be given to prophylactic treatment with any of the agents that have given promising results, specifically theophylline, statins, ascorbic acid, or PGE_1. 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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