

# Evidence-based Approach for Prevention of Radiocontrast-induced Nephropathy

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The frequency of radiocontrast administration is dramatically increasing, with over 80 million doses delivered annually worldwide. Although recently developed radiocontrast agents are relatively safe in most patients, contrast nephropathy (CN) is still a major source of in-hospital and long-term morbidity and mortality, particularly in patients with preexisting kidney disease. Multiple protocols for CN prevention have been studied; however, strict guidelines have not been established, in part because of conflicting efficacy data for most prevention approaches. In this work, we critically review the major trials that have addressed common CN prophylaxis strategies, including type of radiocontrast media, N-acetylcysteine administration, extracellular fluid volume expansion, and hemofiltration/hemodialysis. We conclude with evidence-based recommendations for CN prevention, which emphasize concurrent NaHCO<sub>3</sub> infusion and N-acetylcysteine administration. These guidelines should be helpful to hospitalists, who frequently order radiocontrast studies, and could therefore have a significant impact on prevention of CN. *Journal of Hospital Medicine* 2009;4:500–506. © 2009 Society of Hospital Medicine.

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Since contrast nephropathy (CN) was recognized more than 50 years ago,<sup>1</sup> there have been continuous efforts to chemically modify radiocontrast agents to be less nephrotoxic. Although radiocontrast media have indeed become safer, which reduces the likelihood of CN per procedure, the indications for radiocontrast administration have dramatically increased, since over 80 million doses are delivered in the world annually.<sup>2,3</sup> Furthermore, the number of patients with CN risks, which are mainly chronic renal insufficiency (CRI) and diabetes (Table 1), has also grown. Currently, more than 26 million people are estimated to have CRI in the United States<sup>4</sup> and 200 million people have diabetes worldwide.<sup>5</sup> The combination of increased radiocontrast administration frequency and greater prevalence of at-risk patients is likely to result in continued increases in CN events.

The incidence of CN varies between studies, depending on risk factors of the cohort and definition of CN, but figures have been reported to be as high as 50% in studies enriched with CRI and diabetic patients. However, a very recent study disputes such high incidence rates by demonstrating that patients receiving no radiocontrast media had a similar frequency of serum creatinine increases compared to a comparable group of historical CN patients.<sup>6</sup> This study emphasizes that conventional definitions of CN, eg, 25% increase in serum creatinine above baseline, may be too conservative.

A retrospective study of 7586 patients showed 22% in-hospital mortality in patients who developed CN vs. 1.4% in those who did not, after adjusting for comorbidities. One- and 5-year mortality rates were also higher in the CN group

(12.1% vs. 3.7% and 44.6% vs. 14.5%, respectively).<sup>7</sup> Another study of 1826 patients, who underwent coronary artery intervention procedures, showed that 14.4% developed CN and 0.8% required hemodialysis. Mortality was 1.1% in patients who did not develop CN, 7.1% in those with CN, and 35.7% in the hemodialysis-treated CN group.<sup>8</sup> Moreover, studies by several other groups also support the position that CN is associated with increased in-hospital and long-term mortality.<sup>9–11</sup> Although radiocontrast administration may not be a causal risk factor for mortality, since at-risk patients have a number of comorbidities, radiocontrast media should nevertheless at least be viewed as an important marker of acute kidney injury and death risk.

Despite the enhanced morbidity and mortality associated with CN, there are no strict guidelines for prevention of CN. Part of the reason is that the literature is controversial regarding most prevention strategies. Several interventions are commonly proposed to help prevent CN, including discriminate selection of the type of radiocontrast, N-acetylcysteine, volume expansion with saline and/or NaHCO<sub>3</sub>, and prophylactic hemofiltration. The major purpose of this review is to discuss these different approaches to CN prevention, with the ultimate goal of offering discrete recommendations.

The basis of this semisystematic review was a literature search using the PubMed database ([www.ncbi.nlm.nih.gov/sites/entrez](http://www.ncbi.nlm.nih.gov/sites/entrez)) to identify studies published in English language journals between January 1966 and July 2008 comparing regimens for prophylaxis of CN. Search terms included contrast, radiocontrast, radioiodinated AND nephropathy,

**TABLE 1. Risk Factors for Contrast Nephropathy**

Clear Risks	Probable Risks	Questionable Risks
Estimated GFR <60 mL/minute/1.73 m <sup>2</sup> , especially if due to diabetic nephropathy*	Diabetes mellitus*	Repeat contrast procedures
	Concomitant use of nephrotoxic drugs	Age >75 years
	Hemodynamic instability	Male gender
	Congestive heart failure	Intraaortic balloon pump
	Large contrast volume (>100 mL) <sup>†</sup>	Liver disease
	Intraarterial contrast administration	Peripheral vascular disease
		Hypertension
		Anemia
		Bence-Jones proteinuria <sup>‡</sup>
		Hyperuricemia

**Abbreviations:** CN, contrast nephropathy; CT, computed tomography; GFR, glomerular filtration rate; IVC, inferior vena cava.

\*Diabetes is neither sufficient nor necessary, but amplifies the risk for CN.

<sup>†</sup>Volumes >100 mL are commonly used in diagnostic and therapeutic cardiac catheterizations, peripheral and cerebrovascular angiographies, CT angiography for cardiac imaging and excluding pulmonary embolism. For IVC filter placement, approximately 30 mL is used.

<sup>‡</sup>Risk is negligible with newer generation radiocontrast media and adequate hydration.

nephrotoxicity, renal failure, kidney injury AND N-acetylcysteine, Mucomyst, sodium bicarbonate, NaHCO<sub>3</sub>, hemofiltration, continuous venovenous hemofiltration (CVVH), theophylline, statin, ascorbic acid, dopamine, fenoldopam, adenosine, and endothelin. The total number of articles that met the search criteria exceeded 3000 and over 200 in high profile biomedical journals were scrutinized in detail. The articles cited in this review were independently considered by 2 authors (B.G.A. and J.R.S.) to have the greatest impact.

We report on prophylactic maneuvers that are either commonly considered by nephrology consultants or contain sufficient data to warrant a meta-analysis study. Studies involving statins, ascorbic acid, dopamine analogs, endothelin antagonists, and theophylline were not addressed in this review due to insufficient, inconclusive, or predominantly negative data. Clinical characteristics and pathogenesis of CN, which include vasoconstriction, ischemia, production of oxygen free radicals, tubular cell apoptosis, and intratubular obstruction, are also not discussed in detail, but have recently been reviewed.<sup>12</sup>

### Risk Associated with Different Types of Radiocontrast Media

There are 3 generations of radiocontrast media: hyperosmolar (1400–1800 mosm/kg), low osmolar (500–850 mosm/kg) and isoosmolar (290 mosm/kg). Note that the low osmolar agents have lower osmolarity relative to the hyperosmolar agents, but are still hyperosmolar compared to serum. Multiple studies have compared effects of radiocontrast with different osmolarities.

The Iohexol Cooperative Study was a double-blind, randomized, controlled trial (RCT) that randomized 1196 patients to Iohexol (low osmolarity) or diatrizoate (hyperosmolar). Definition of CN was a rise in serum creatinine by >1 mg/dL within 48 to 72 hours after the radiocontrast exposure. Results were in favor of the Iohexol group (3% developed CN vs. 7% in the diatrizoate group; *P* = 0.002). Subgroup analysis of patients with CRI and CRI plus diabetes also revealed less CN in the Iohexol vs. diatrizoate groups (7% vs. 16% and 12% vs. 27%, respectively).<sup>13</sup>

An earlier non-RCT of 303 patients undergoing femoral angiography compared Iohexol/Ioxaglate (both are low osmolar) to diatrizoate (hyperosmolar). Six different CN definitions were used. Each comprised a combination of different magnitudes of rise of serum creatinine over various periods of time. Overall, the incidence of CN was 7% in the low osmolar group vs. 26% in the hyperosmolar group (*P* = 0.001). In subgroup analysis of patients with CRI, and of patients with diabetes, less CN was again observed with low osmolar agents (10% vs. 41%, *P* = 0.017, in the CRI group; and 10% vs. 31%, *P* = 0.012, in the diabetes group). Analysis of subjects with baseline serum creatinine <1.5 mg/dL showed no differences between the 2 groups, emphasizing that prior CRI is an important CN risk factor.<sup>14</sup>

The RECOVER study was a double-blind RCT of 300 patients undergoing coronary angiography, who were randomized to iodixanol (isoosmolar) or Ioxaglate (low osmolarity). CN was defined as a rise in serum creatinine by >25% or 0.5 mg/dL at 24 and 48 hours. CN incidence was 7.9% in the iodixanol group vs. 17% in the Ioxaglate group (*P* = 0.021). Subgroup analyses of patients stratified by severe CRI, diabetes, and contrast volume also favored iodixanol.<sup>15</sup> In a similarly designed, double-blind RCT involving 129 patients with diabetes and CRI randomized to iodixanol or Iohexol, CN developed in 3% of iodixanol group vs. 26% in the Iohexol group (*P* = 0.002).<sup>16</sup> These results were further supported by a very recent double-blind RCT comparing iodixanol to Iopromide (low osmolar) in 117 patients with baseline serum creatinine ≥1.5 mg/dL undergoing CT scans. The incidence of serum creatinine increases of ≥0.5 mg/dL or ≥25% above baseline or glomerular filtration rate (GFR) reduction of ≥5 mL/minute was significantly lower in the iodixanol group (*P* = 0.04, 0.01, and 0.04 respectively).<sup>17</sup>

In contrast to these reports, 2 double-blind RCTs showed no differences in CN incidence between iodixanol and low osmolar agents. One study compared iodixanol to Iopromide in 64 patients undergoing intravenous pyelography (IVP),<sup>18</sup> and the other included 16 nondiabetic patients with CRI and compared iodixanol to Iohexol.<sup>19</sup> However, because of the small sample sizes, it is likely that neither study is adequately powered to detect differences in outcome between the 2 types of radiocontrast media.

Given the importance of the issue and conflicting results from individual studies, a meta-analysis of 16 double-blind RCTs was performed.<sup>20</sup> This study included 2727 patients

undergoing angiography, compared iodixanol (isoosmolar) to a variety of low osmolar agents, and demonstrated that iodixanol was less nephrotoxic compared to the low osmolarity agents in CRI patients (2.8% vs. 8.4%;  $P = 0.001$ ) and in patients with CRI plus diabetes (3.5% vs. 15.5%;  $P = 0.003$ ). Independent predictors of CN were CRI, CRI plus diabetes, and the use of low-osmolarity media, whereas diabetes, age, and radiocontrast volume were not statistically significant independent predictors.<sup>20</sup>

Taken together, we conclude that isoosmolar media represents the lowest risk for CN. An additional benefit is that isoosmolar media, on the basis of diminished osmotic load, is less likely to precipitate extracellular fluid volume overload, which is particularly germane for patients with CRI, who have diminished capacity to excrete solute loads. Therefore, we recommend using isoosmolar media, particularly in patients at high risk for CN, such as those with CRI, especially due to diabetic nephropathy.

### Oral N-Acetylcysteine

Based primarily upon in vitro evidence, N-acetylcysteine (NAC) may theoretically prevent CN by direct antioxidant and vasodilatory effects. However, in vivo, NAC is rapidly metabolized and inactivated by the liver. Therefore, it has been postulated that the mechanism of action may be indirect, and the cysteine metabolite of NAC may stimulate glutathione synthesis, which then inhibits cellular oxidation.<sup>21</sup>

The first clinical trial to address the prophylactic role of NAC in CN was an RCT of 83 patients with CRI (mean serum creatinine [Cr] = 2.4) undergoing CT scans, who were randomized to NAC plus 0.45% NaCl vs. placebo and 0.9% NaCl.<sup>22</sup> The NAC dose was 600 mg orally twice daily for 2 doses before and 2 doses after the procedure. Intravenous fluids were started 12 hours before and stopped 12 hours after the procedure and infused at a rate of 1 ml/kg/hour. CN definition was rise in serum creatinine by >0.5 mg/dL at 48 hours. The results were statistically significant, with a relative risk of CN = 0.1 (95%CI, 0.02–0.9) in subjects treated with NAC.

There have been many subsequent reports that have evaluated NAC in small numbers of patients with mild to moderate CRI. In general, results from these trials have been inconsistent, which has led to several meta-analyses to delineate NAC efficacy in CN prevention. The most recent and largest meta-analysis included 26 NAC RCTs, and revealed a statistically significant benefit from NAC (relative risk [RR] = 0.62; 95%CI, 0.44–0.88).<sup>23</sup> Twelve other meta-analyses, which incorporated fewer studies, have been published,<sup>24–35</sup> and 7 of the 12 reported a benefit from NAC.<sup>25,27,29,30,32,34,35</sup>

Although meta-analysis is considered the most accepted strategy to define conclusions from multiple trials, conflicting results between NAC meta-analyses highlight the possibility that this approach may still not provide resolution to clinical questions, especially when inclusion criteria differ

between meta-analyses. Therefore, as discussed by Bagshaw et al.,<sup>36</sup> meta-analyses are not always a panacea, and should be avoided if the trials to be included exhibit significant statistical or clinical heterogeneity, as is the case with studies involving NAC prophylaxis of CN. Finally, because meta-analyses require pooling of data from published studies, which tend to be positive, the possibility of publication bias exists.

In summary, conclusions from trials to assess efficacy of oral NAC in the prevention of CN have been inconsistent, though there has been a general trend toward benefit. Factors contributing to inconsistent results include variable definitions of CN, degree of CRI and diabetes in the cohort, amount and type of contrast used, NAC dosing and intravenous hydration protocols. As a result, a large multicenter RCT would certainly be helpful. However, the size of such trial might be cost-prohibitive, and unlikely to be underwritten by the pharmaceutical industry because the patent for NAC has expired.<sup>36</sup>

### Intravenous NAC

In addition to the vast literature on oral NAC for CN prophylaxis, there are now studies that have also evaluated efficacy of intravenous NAC. In one of the largest double-blind RCTs,<sup>37</sup> 487 patients (mean baseline serum creatinine = 1.6 mg/dL) were randomized to NAC 500 mg intravenously vs. placebo before cardiac catheterization. Both groups received the same hydration protocols. The study was stopped when an interim analysis determined that there was no advantage to NAC (CN incidence, which was defined as a decrease in creatinine clearance by >5 mL/minute at days 1 to 8 post-procedure, was 23.3% vs. 20.7% in the placebo group).

The RAPPID study examined higher intravenous NAC doses in 80 patients undergoing cardiac catheterization.<sup>38</sup> Subjects in this study were randomized to either NAC (150 mg/kg in 500 mL 0.9% NaCl before procedure and then 50 mg/kg in 500 mL 0.9% NaCl over 4 hours after procedure) or 0.9% NaCl 12 hours before and 12 hours after procedure. Despite the relatively small study size, intravenous NAC demonstrated a significant benefit in the prevention of CN (RR = 0.28;  $P = 0.045$ ) defined as rise in serum creatinine by >25% at 2 or 4 days postexposure. Hypersensitivity-like reactions were observed in 14.5% of patients receiving intravenous NAC, but symptoms were easily recognized and managed.<sup>38</sup>

A recent study of 354 patients undergoing primary angioplasty evaluated the combination of intravenous and oral NAC in different doses.<sup>39</sup> Patients were randomized to 3 groups: (1) NAC 600 mg intravenously once before procedure and then 600 mg orally twice daily for 48 hours; (2) NAC 1200 mg intravenously once before procedure and then 1200 mg orally twice daily for 48 hours; or (3) placebo. The primary outcome was increase in Cr by >25% and secondary outcomes were in-hospital death and a composite score that included death and need for renal replacement

therapy. Results were significantly in favor of the 1200-mg NAC regimen across all outcomes ( $P = <0.001$ , 0.02, and 0.002, respectively). It should be emphasized that this study was restricted to patients undergoing primary angioplasty, which is an emergent procedure. As a result, implementation of this protocol would necessarily require rapid administration of intravenous NAC prior to the procedure, which might even require maintenance of NAC stocks within the catheterization laboratory.

Because there is a trend toward benefit from oral NAC and the benefit from intravenous NAC in trials from limited settings, and both NAC formulations are inexpensive and safe, we recommend that NAC should be included in CN prophylaxis protocols.

### Extracellular Fluid Volume Expansion

Since publication of work by Solomon et al.,<sup>40</sup> which demonstrated a benefit of intravenous hydration with 0.45% NaCl in the prevention of CN in a group of CKD patients, it has been considered standard practice to prescribe intravenous fluid regimens for CN prophylaxis in high-risk subjects. In the largest study to test the effect of different hydration protocols for CN prevention, Mueller et al.<sup>41</sup> randomized 1620 patients with normal baseline serum creatinine to intravenous 0.9% NaCl vs. 0.45% NaCl. The definition of CN was rise in serum creatinine by  $>0.5$  mg/dL at 48 hours and the incidence was 0.7% for the 0.9% NaCl group and 2% for the 0.45% NaCl group ( $P = 0.04$ ).

More recently, several trials have examined the relative efficacy of intravenous NaCl vs.  $\text{NaHCO}_3$  for CN prophylaxis. In the first  $\text{NaHCO}_3$  RCT, Merten et al.<sup>42</sup> compared 0.9%  $\text{NaHCO}_3$  to 0.9% NaCl infusion in a population with a mean serum creatinine of 1.8 mg/dL. Both groups received 3 mL/kg intravenous bolus over 1 hour before the radiographic procedure followed by 1 mL/kg/hour for 6 hours. Urine pH was measured to confirm alkalization of urine in the  $\text{NaHCO}_3$ -treated patients and the primary end point was increase in serum creatinine by  $>25\%$  within 48 hours. The study was terminated early (after enrollment of 119 patients) when the interim analysis showed CN incidence was 1.7% in the  $\text{NaHCO}_3$  group vs. 13.6% in the NaCl group ( $P = 0.02$ ).

These results were corroborated in the recent REMEDIAL trial,<sup>43</sup> which enrolled 326 patients with serum creatinine  $>2$  mg/dL, who were randomized to 1 of 3 arms. One group received intravenous saline (0.9% NaCl for 12 hours before and 12 hours after the procedure) and oral NAC; a second group received intravenous  $\text{NaHCO}_3$  (3 mL/kg intravenous bolus over 1 hour before the radiographic procedure followed by 1 mL/kg/hour for 6 hours) and oral NAC; and a third group received intravenous 0.9% NaCl plus oral NAC and ascorbic acid. Patients had similar baseline characteristics and the primary end point was an increase in serum creatinine by  $>25\%$  within 48 hours. The best results were observed in the  $\text{NaHCO}_3$  plus NAC group; 1.9% developed

CN in this group vs. 9.9% in the NaCl plus NAC group vs. 10.3% in the NaCl plus NAC plus ascorbic acid group ( $P = 0.019$ ). Three additional prospective but smaller studies also showed the superiority of  $\text{NaHCO}_3$ .<sup>44–46</sup>

In contrast to studies supporting a role for prophylactic  $\text{NaHCO}_3$ , a recent RCT showed no superiority of  $\text{NaHCO}_3$  infusion regimens.<sup>47</sup> In this trial, 352 patients undergoing coronary angiography were randomized to receive either  $\text{NaHCO}_3$  or 0.9% NaCl. Both solutions were administered at rates of 3 mL/kg for 1 hour before the procedure and 1.5 mL/kg/hour for 4 hours postprocedure. The primary end point ( $>25\%$  decrease in estimated GFR during the first 4 days after contrast exposure) was met in 13.3% of  $\text{NaHCO}_3$  group vs. 14.6% of the 0.9% NaCl group ( $P = 0.82$ ). Moreover, there were no differences in the rates of secondary outcomes, which included death, dialysis, and cardiovascular and cerebrovascular events.

Results from a very recent retrospective cohort study of 7977 patients demonstrated that  $\text{NaHCO}_3$  infusion was associated with increased risk of CN compared to no treatment (odds ratio [OR] = 3.1;  $P < 0.001$ ), whereas NAC alone or in combination with  $\text{NaHCO}_3$  was associated with no significant difference in the incidence of CN.<sup>48</sup> However, multiple weaknesses associated with the retrospective study design, such as inclusion of few patients at high CN risk, and acceptance of serum creatinine values within 7 days before and after the contrast procedure, which likely captures causes of acute kidney injury other than CN, preclude abandonment of  $\text{NaHCO}_3$  prophylaxis for CN solely on the basis of this study.

In an effort to resolve the conflicting  $\text{NaHCO}_3$  prophylaxis literature, a meta-analysis was recently conducted.<sup>49</sup> This study encompassed 1307 patients enrolled in 7 RCTs that examined outcomes for  $\text{NaHCO}_3$  vs. saline prevention of CN. The main finding was a significant benefit of  $\text{NaHCO}_3$  for protection against CN (RR = 0.37;  $P = 0.005$ ). No benefit of  $\text{NaHCO}_3$  infusion could be shown for postprocedure renal replacement therapy or death.

Therefore, based upon the results of multiple prospective trials, the recent meta-analysis, the relative safety of  $\text{NaHCO}_3$  infusion with appropriate monitoring, and a plausible biological mechanism whereby bicarbonate may have antioxidant properties and scavenge oxygen-derived free radicals, which have been implicated in CN pathogenesis,<sup>50</sup> we advocate a prophylactic regimen employing  $\text{NaHCO}_3$  for patients at high risk for CN.

### Renal Replacement Therapies

Two studies have been conducted by the same group (Marenzi et al.<sup>51,52</sup>) to examine efficacy of continuous hemofiltration (CVVH) in preventing CN (hemofiltration clears solute by convection, and involves administration of a  $\text{HCO}_3^-$ -rich replacement solution, whereas hemodialysis clears solute by both diffusion and convection, and there is routinely no replacement fluid). In the first study,<sup>51</sup> 114 patients with

baseline serum creatinine greater than 2 mg/dL undergoing coronary angiography were randomized to hemofiltration vs. 0.9% NaCl infusion. Isovolemic hemofiltration was implemented for 4 to 6 hours before and 18 to 24 hours after the radiographic procedure. The primary endpoint was increase in creatinine by >25% within 72 hours. CN incidence was 5% in the hemofiltration group vs. 50% in the 0.9% NaCl group ( $P < 0.001$ ). The secondary outcomes including in-hospital mortality, 1-year mortality and temporary renal replacement were also superior in the hemofiltration group. In the second study, the same investigators compared 2 different hemofiltration protocols, using the same definition of CN.<sup>52</sup> Patients with baseline creatinine clearance <30 mL/minute ( $n = 92$ ) were randomized to 0.9% NaCl infusion, postprocedure isovolemic hemofiltration only, or preprocedure plus postprocedure hemofiltration (same protocol as previous study). The incidence of CN was significantly lower in the preprocedure plus postprocedure hemofiltration group (3% vs. 26% in the postprocedure hemofiltration group vs. 40% in the 0.9% NaCl without hemofiltration group;  $P = 0.0001$ ). The preprocedure plus postprocedure hemofiltration group also had reductions in in-hospital mortality and temporary renal replacement therapy rates.

Although the mechanism of hemofiltration prevention of CN is unknown, it is certainly not enhanced clearance of contrast material, inasmuch as hemofiltration was discontinued during the angiography procedure in all protocols, and radiocontrast was therefore not cleared by hemofiltration until the process was reinstated. Furthermore, the second study indicates that the major benefit was derived from the preprocedure hemofiltration component. Contributing factors might be control of extracellular pH and redox potential with bicarbonate replacement fluid during hemofiltration. Important confounding issues to consider are that patients receiving hemofiltration were in controlled, monitored settings and thus received more intensive care than the hydration group, and that serum creatinine, the major outcome parameter, is cleared by hemofiltration. Before hemofiltration can be recommended as routine prophylactic therapy for CN, the data will need to be corroborated by other groups, preferably involving larger numbers of study subjects and including cost-benefit analyses.

Multiple small studies have examined the possibility that dialysis immediately following radiocontrast exposure could prevent CN, presumably by accelerating radiocontrast clearance. Most of these reports were negative, including a well-designed meta-analysis of RCTs, which showed no benefit of hemodialysis.<sup>53</sup> Of note, one report suggested that hemodialysis might be potentially harmful.<sup>54</sup> The single prospective trial that showed benefit from prophylactic hemodialysis analyzed 82 patients with advanced CRI (baseline creatinine clearance ~13 mL/minute) referred for coronary angiography.<sup>55</sup> These subjects were randomly assigned to intravenous 0.9% NaCl and hemodialysis vs. intravenous 0.9% NaCl alone. Subsequent renal replacement therapy was required in 35%

of control patients and in only 2% in the prophylactic dialysis group. One potential limitation of this study is that the investigators were more cognizant of volume status in the hemodialysis group to avoid fluid shifts and volume depletion during dialysis, while the control group appeared to experience no comparable intravascular volume management. Moreover, this study was conducted in patients with extremely advanced renal insufficiency, and therefore does not reflect the vast majority of patients at risk for CN.

## Conclusions

CN is associated with increased morbidity and mortality, and efforts to minimize CN are therefore warranted. However, the overwhelming majority of CN trials were designed to investigate the effects of prophylaxis strategies on surrogate endpoints for estimates of GFR. Therefore, conclusions regarding the effect of these regimens on definitive outcomes, such as death and vascular events, cannot be drawn. On balance, there is evidence that oral and intravenous NAC, as well as extracellular volume expansion with intravenous  $\text{NaHCO}_3$  are effective measures to prevent CN, whereas the data for renal replacement therapies are more equivocal. We emphasize though, that the literature on this topic is vast, and includes a large number of conflicting studies, including multiple meta-analyses. As a result, we refrain from being too dogmatic about the best approach, and therefore cautiously offer the following recommendations for prevention of CN.

The first step is to identify high-risk patients, who are most likely to benefit from prophylaxis (Table 1). Although risk stratification was not the focus of this review, Mehran et al.<sup>56</sup> have developed a scoring system to quantitatively predict CN risk, with weighted parameters including CRI, diabetes, radiocontrast volume, age, hypotension, congestive heart failure, treatment with an intraaortic balloon pump, and anemia. For low-risk patients, hydration with saline is probably adequate. For high-risk patients, it would be prudent to initially consider whether sufficient information could be obtained from an alternative, noncontrasted radiologic procedure. If not, it would behoove the prescribing physician to then treat modifiable risk factors, as well as to discontinue potentially nephrotoxic medications.

In high-risk patients undergoing radiocontrast procedures, we recommend using NAC and volume expansion with  $\text{NaHCO}_3$  (Table 2). Although the evidence for this "combined approach" is limited,<sup>43</sup> we believe it is biologically consistent, since the rationale for both strategies is primarily modification of redox state and inhibition of oxygen free radical generation. Because NAC formulations are generally effective, safe and inexpensive (\$0.04 for 600 mg oral NAC and \$24 for 1200 mg intravenous NAC at our hospital), we recommend the protocol used by Marenzi et al.,<sup>39</sup> NAC 1200 mg intravenously once before procedure and then 1200 mg orally twice daily for 48 hours, as prophylaxis for all contrast procedures in high-risk patients. However, we

**TABLE 2. Contrast Nephropathy Prevention Strategy in High-Risk Patients**

- Minimize radiocontrast dose.
- Isoosmolar radiocontrast media preferred.
- Intravenous NaHCO<sub>3</sub> at 3 mL/kg/hour for 1 hour prior to radiocontrast exposure, then 1 mL/kg/hour for 6 hours after.
- Intravenous N-acetylcysteine 1200 mg before procedure, then 1200 mg orally twice daily for a total of 4 doses.
- If intravenous N-acetylcysteine is not available, then N-acetylcysteine 600–1200 mg orally for 2 doses before and 2 doses after procedure.
- If already undergoing acute dialysis with catheter vascular access, consider CVVH 6 hours before and for 24 hours after procedure.

**Abbreviations:** CN, contrast nephropathy; CVVH, continuous venovenous hemofiltration.

recognize that this regimen would require formal evaluation in procedures other than emergent coronary artery angioplasty before it could be enthusiastically endorsed. Therefore, if intravenous NAC is not available and/or the procedure is not emergent, NAC 600–1200 mg orally twice a day, 2 doses before and 2 doses after the procedure would be a rational alternative. For the NaHCO<sub>3</sub> infusion, we recommend 3 mL/kg for 1 hour before the procedure, followed by 1 mL/kg/hour for 6 hours after.

Hemofiltration is labor-intensive, expensive, and not readily available in all hospitals that renders it difficult to endorse as a definitive or routine CN prophylaxis modality. However, if a patient is already undergoing acute dialysis with catheter vascular access, it would be reasonable to consider CVVH 6 hours before and for 24 hours after the procedure (Table 2).

For high-risk patients, we recommend minimizing the radiocontrast dose (reviewed in Ref. 57). Although the dose has not consistently been identified as a risk factor (Table 1), we envision no harm in reducing the dose, particularly if adequate information can be obtained by other means, eg, coronary angiogram accompanied by an echocardiogram, rather than a ventriculogram. We would also consider the use of isoosmolar media in high-risk patients, since the data are relatively compelling.<sup>20</sup> Low doses of isoosmolar media should be particularly beneficial to patients with preexisting hypertension or congestive heart failure, for which the osmotic load and excess extracellular volume expansion might be deleterious. However, because isoosmolar media is expensive, a detailed cost-benefit analysis would be required before definitive recommendations could be made, especially for patients at lower risk for CN. Finally, because of the complex literature, as well as budgetary issues, we encourage communication between the physician ordering the contrast study and the operator (radiologist or cardiologist) concerning the type of procedure and contrast media to be used.

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