Contrast-Induced Nephropathy
A Clinical and Evidence-Based Approach

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Contrast medium–induced nephropathy (CIN) is a common cause of acute renal dysfunction. During the past few years, several publications have provided clinical and experimental data on this topic. Our review focuses on 4 major concerns of CIN relevant in clinical practice: (1) What is the evidence that CIN is a clinically relevant and a dangerous condition for the patient? (2) Is there a difference in CIN rate among different contrast media, and how is that related to the physicochemical properties of different available contrast media? (3) What is the evidence that periprocedural hydration is an effective, appropriate, and safe method to prevent CIN? (4) What is the evidence for the use of a drug, in particular acetylcysteine, to prevent CIN?

Clinical Relevance
CIN has gained increased attention in the clinical setting, particularly during cardiac intervention but also in many other radiological procedures in which iodinated contrast media are used. There is at present good clinical evidence from well-controlled randomized studies that CIN is a common cause of acute renal dysfunction.3–7 CIN is the acute deterioration of renal function after parenteral administration of radiocontrast media in the absence of other causes. CIN is generally defined as an increase in serum creatinine concentration of >0.5 mg/dL (≥44 μmol/L) or 25% above baseline within 48 hours after contrast administration.3–7

Although the exact mechanisms of CIN have yet to be fully elucidated, several causes have been described. Increased adenosine−, endothelin−, and free radical−induced vasoconstriction and reduced nitric oxide− and prostaglandin−induced vasodilatation have been observed. These mechanisms cause ischemia in the deeper portion of the outer medulla, an area with high oxygen requirements and remote from the vasa recta supplying the renal medulla with blood. Contrast agents also have direct toxic effects on renal tubular cells, causing vacuolization, altered mitochondrial function, and apoptosis.8 Atopy does not play a role in the pathogenesis of CIN.

The incidence of CIN in the general population has been calculated to be <2%. In high-risk patients, ie, patients with chronic renal impairment, diabetes mellitus, congestive heart failure, and older age, the incidence has been calculated to be >20% to 30%.3–7 CIN has been associated with increased morbidity, extended length of hospital stay, and increased costs.9 Several risk factors have been described for CIN.10–12 A risk score for prediction of CIN after percutaneous coronary intervention has been reported by Mehran et al.12 That risk score includes hypotension (5 points, if systolic blood pressure <80 mm Hg for at least 1 hour requiring inotropic support), use of intra-aortic balloon pump (5 points), congestive heart failure (5 points, if class III/IV by New York Heart Association classification or history of pulmonary edema), age (4 points, if >75 years), anemia (3 points, if hematocrit <39% for men and <36% for women), diabetes mellitus (3 points), contrast media volume (1 point per 100 mL), estimated glomerular filtration rate (GFR; GFR in mL/min per 1.73 m²; 2 points, if GFR 60 to 40; 4 points, if GFR 40 to 20; 6 points, if GFR <20). A risk score of <6, 6 to 10, 11 to 16, and >16 indicates a risk for CIN of 7.5%, 14%, 26%, and 57%, respectively.12

Is There a Difference in CIN Between Different Contrast Media? How Is That Related to Their Physicochemical Properties?

Physicochemical Properties of Contrast Agents
In 1968 Almén proposed new, low-toxicity, nonionic, monomeric and dimeric contrast media, and since then the toxicity of different contrast media has mainly been attributed to their osmolality, viscosity, and chemotoxicity.8,16–21 Contrast media today are commonly divided into high-osmolar, low-osmolar, and iso-osmolar contrast media. The osmolality value is often expressed in terms of the ratio...
between the number of iodine atoms and the number of dissolved particles. The higher the ratio, the better is the attenuation of x-rays because there are more iodine atoms for fewer particles of contrast agent. Contrast agents with a ratio of 1:5:1 are monomeric ionic and hyperosmolar with an osmolality in the range of 1000 to 2000 mOsm/kg. Nonionic monomeric or ionic dimeric contrast media with a ratio of 3:1 are low-osmolar contrast media, with an osmolality in the range of 290 to 300 mOsm/kg, ie, iso-osmolar with plasma. Iso-osmolar nonionic contrast media have reduced osmolality because of the creation of a dimer, linking 2 molecules of contrast agent together through a common side chain and thereby increasing the size of the molecule in solution. On the basis of experimental studies in rats in particular, it has been argued that the high viscosity of the dimeric iso-osmolar contrast media could be a disadvantage. Additionally, direct measurements in rats with micro-electrodes showed a similar reduction of the medullary oxygen tension after administration of either the low-osmolar contrast agent iopromide (viscosity ≈5 mPa·s) or the iso-osmolar contrast agent iotrolan (viscosity ≈8.5 mPa·s).

Direct chemical toxicity is mainly dependent on the physicochemical properties of contrast media. A recent in vitro study revealed that in addition to the osmolality of the agent, a direct cytotoxic effect of the molecule could contribute to its cytotoxic effects. However, when the agent was dissolved to equal urine concentrations, no difference in cytotoxicity could be demonstrated between the dimeric iso-osmolar contrast media and the low-osmolar contrast media. When, however, the agents were administered in iso-osmolar concentrations, the dimeric contrast media had a higher cytotoxic effect than the low-osmolar contrast media. One should keep in mind that in clinical investigations a patient usually receives a contrast agent in equal iodine concentrations and that in the human kidney the molar concentration of the dimer is only half that of a low-osmolar contrast agent.

### Clinical Studies Comparing High- and Low-Osmolar Contrast Media

With the introduction of low-osmolar and iso-osmolar contrast media, a reduction in the incidence of CIN has been observed. Low-osmolar contrast media have gained widespread clinical acceptance because of fewer adverse effects than high-osmolar contrast media, particularly in high-risk patients with an elevated preprocedural serum creatinine. Furthermore, for patients with preexisting renal insufficiency, ie, patients with preexisting renal insufficiency alone or combined with diabetes mellitus had a significantly lower risk of CIN when low-osmolar contrast media are used. Subsequently, a meta-analysis of 25 trials with available data revealed a pooled odds ratio of CIN with low-osmolar contrast media of 0.61 (95% CI, 0.48 to 0.77) times that with high-osmolar contrast media. Furthermore, for patients with preexisting renal insufficiency, this odds ratio was 0.5 (95% CI, 0.36 to 0.68), whereas it was 0.75 (95% CI, 0.52 to 1.10) in patients without prior renal insufficiency.

### Clinical Studies Comparing Iso-Osmolar and Low-Osmolar Contrast Media

Several studies have included both iso-osmolar and low-osmolar contrast media when investigating the incidence of CIN.
Evidence for Periprocedural Hydration

Textbooks recommend periprocedural hydration as a simple and effective means to prevent CIN. However, no large prospective, randomized trial of deliberate hydration versus no intervention for the prevention of CIN has been conducted, and therefore several questions remain. An early study by Eisenberg et al. showed that hydration with 550 mL normal saline plus 250 mL heparinized saline flush per hour prevented CIN in 537 patients undergoing cerebral, abdominal, or peripheral angiography with the use of high-osmolar contrast media. However, that retrospective study lacked randomization and an appropriate control group. Surprisingly, another early study on 364 patients undergoing angiography did not find a preventive effect of hydration on CIN.

Should fluids be administered intravenously or orally? On the one hand, Trivedi et al. compared the effects of intravenous normal saline at a rate of 1 mL/kg per hour for 24 hours beginning 12 hours before contrast administration versus hydration with unrestricted oral fluids on the incidence of CIN. One of 27 patients (3.7%) in the intravenous saline group suffered from CIN compared with 9 of 26 patients (34.6%) in the orally hydrated group (relative risk, 0.11; 95% CI, 0.02 to 0.79; P = 0.005). On the other hand, a randomized prospective study in 36 patients showed that the administration of 0.45% normal saline given intravenously at a rate of 75 mL/h for 24 hours beginning 12 hours before contrast administration had similar effects on the increase in serum creatinine compared with oral hydration with 1000 mL clear liquid over 10 hours plus 0.45% normal saline at 300 mL/h for 6 hours beginning just before contrast administration.

Can a forced diuresis with maintenance of intravascular volume reduce CIN? At least 2 prospective, randomized trials addressed that question. Solomon et al. showed that CIN in patients with preexisting renal insufficiency undergoing percutaneous coronary angiography occurred in 3 of 28 patients (10.7%) who received intravenous 0.45% saline. By contrast, CIN developed in 7 of 25 patients (28.0%) who received intravenous saline plus 25 g mannitol (P = 0.16 compared with saline) and in 10 of 25 patients (40.0%) who received intravenous saline plus 80 mg furosemide (P = 0.02 compared with saline). Stevens et al. showed that in patients with preexisting renal insufficiency and undergoing percutaneous coronary intervention, CIN occurred in 17 of 55 patients (30.9%) who received intravenous fluid hydration (0.45% saline at a rate of 150 mL/h), in 7 of 21 patients (33.3%) who received intravenous 154 mmol/L sodium bicarbonate but in 8 of 59 patients (13.6%) who received intravenous fluid hydration plus 1 mg/kg furosemide plus 3 µg/kg/min dopamine, and in 7 of 22 patients (31.8%) who received intravenous fluid hydration plus furosemide plus dopamine plus mannitol, showing no significant differences between all groups. From these studies, it can be concluded that forced diuresis is not superior compared with hydration with saline alone to prevent CIN. Neither mannitol nor furosemide nor dopamine offered any additional benefit beyond the hydration protocol.

Which type of fluid should be used for periprocedural hydration? In a large, prospective, randomized trial, 5 of 685 patients (0.7%) given isotonic 0.9% saline but 14 of 698 patients (2.0%) given 0.45% saline developed CIN (P = 0.042 by χ² test). Merten et al. showed in patients with preexisting renal insufficiency undergoing diagnostic or interventional procedures requiring low-osmolar contrast media that CIN occurred in 1 of 60 patients (1.7%) receiving intravenous 154 mmol/L sodium bicarbonate but in 8 of 59 patients (13.6%) who received intravenous 154 mmol/L sodium chloride (relative risk, 0.12; 95% CI, 0.02 to 0.95; P = 0.02).

In summary, despite the fact that formal prospective, randomized studies in humans proving the superiority of preeminent hydration are lacking, current limited evidence supports periprocedural hydration with preferably intravenous administration of 0.9% isotonic saline or an isotonic sodium bicarbonate solution, without furosemide, mannitol, or dopamine.

Evidence for Prevention of CIN by Drugs or Other Procedures

Acetylcysteine: Randomized Controlled Trials

Because of its favorable side effect profile, low costs, and some positive results of randomized studies, acetylcysteine...
has gained favor in clinical practice as a preventive therapy in high-risk groups, ie, patients with preexisting renal insufficiency.5 Trials performed over the past 5 years with this drug, however, have provided conflicting results. Table 2 summarizes data from these prospective, randomized trials.42–66 Several prospective, randomized trials showed that the administration of acetylcysteine along with hydration significantly reduced CIN in high-risk patients, whereas other trials

**TABLE 2. Randomized Trials Evaluating Use of Acetylcysteine for Prevention of CIN**

<table>
<thead>
<tr>
<th>First Author and Reference</th>
<th>Year</th>
<th>Pt No.</th>
<th>Diabetes, %</th>
<th>Procedure</th>
<th>Acetylcysteine Dose and Duration, d</th>
<th>Baseline Serum Creatinine, mg/dL</th>
<th>Placebo Group, Incidence of CIN, n/N (%)</th>
<th>Acetylcysteine Group, Incidence of CIN, n/N (%)</th>
<th>ARR, %</th>
<th>RR</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamian42</td>
<td>2002</td>
<td>47</td>
<td>33-57</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID</td>
<td>2.1</td>
<td>9/42 (21)</td>
<td>1/35 (3)</td>
<td>18 0.13 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baker43</td>
<td>2003</td>
<td>80</td>
<td>41-44</td>
<td>Coronary angiography + PCI</td>
<td>IV 150 mg/kg, before; plus 50 mg/kg for 4 h</td>
<td>1.8</td>
<td>8/39 (21)</td>
<td>2/41 (5)</td>
<td>16 0.24 0.045</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Briguori44 (subgroup of CM &lt;140 mL)</td>
<td>2002</td>
<td>120</td>
<td>NA</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID, 2 d</td>
<td>NA</td>
<td>5/60 (8)</td>
<td>0/60 (0)</td>
<td>8 0 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Briguori45</td>
<td>2004</td>
<td>223</td>
<td>43-41</td>
<td>Coronary angiography + PCI</td>
<td>Standard dose 600 mg BID, 2 d; double dose 1200 mg BID, 2 d</td>
<td>1.6</td>
<td>(Standard dose) 12/109 (11)</td>
<td>(Double dose) 13/95 (14)</td>
<td>49/114 (4)</td>
<td>7 0.32 0.04</td>
<td></td>
</tr>
<tr>
<td>Diaz-Sandoval46</td>
<td>2002</td>
<td>54</td>
<td>21</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID, 2 d</td>
<td>1.6</td>
<td>13/29 (45)</td>
<td>2/25 (8)</td>
<td>37 0.20 0.01</td>
<td></td>
<td></td>
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<tr>
<td>Efrati48</td>
<td>2003</td>
<td>49</td>
<td>53</td>
<td>Coronary angiography + PCI</td>
<td>1000 mg BID, 2 d</td>
<td>1.5</td>
<td>2/25 (5)</td>
<td>0/24 (0)</td>
<td>5 0 0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kay49</td>
<td>2003</td>
<td>200</td>
<td>36-39</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID, 2 d</td>
<td>1.4</td>
<td>12/98 (12)</td>
<td>4/102 (4)</td>
<td>8 0.32 0.03</td>
<td></td>
<td></td>
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<tr>
<td>MacNeil50</td>
<td>2002</td>
<td>140</td>
<td>NA</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID, 2 d</td>
<td>1.9</td>
<td>7/22 (32)</td>
<td>1/21 (5)</td>
<td>27 0.15 0.046</td>
<td></td>
<td></td>
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<tr>
<td>Minner51</td>
<td>2004</td>
<td>192</td>
<td>52-50</td>
<td>Coronary angiography + PCI</td>
<td>1200 mg BID, 2 d; vs fenoldopam 0.10 μg/kg per minute</td>
<td>1.6 (Fenoldopam)</td>
<td>13/95 (14)</td>
<td>4/97 (4)</td>
<td>10 0.30 0.02</td>
<td></td>
<td></td>
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<tr>
<td>Shyu52</td>
<td>2002</td>
<td>121</td>
<td>64-63</td>
<td>Coronary angiography + PCI</td>
<td>400 mg BID, 2 d</td>
<td>2.8</td>
<td>15/61 (25)</td>
<td>2/60 (3)</td>
<td>22 0.14 0.001</td>
<td></td>
<td></td>
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<tr>
<td>Tepel55</td>
<td>2000</td>
<td>83</td>
<td>33</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID, 2 d</td>
<td>2.4</td>
<td>9/42 (21)</td>
<td>1/41 (2)</td>
<td>19 0.11 0.01</td>
<td></td>
<td></td>
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<tr>
<td>Allaqaband54</td>
<td>2002</td>
<td>85</td>
<td>50</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID, 2 d</td>
<td>2.1</td>
<td>6/40 (15)</td>
<td>8/45 (18)</td>
<td>-3 1.19 0.78</td>
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<tr>
<td>Boccalandro53</td>
<td>2003</td>
<td>179</td>
<td>61-49</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID, 2 d</td>
<td>1.9</td>
<td>13/106 (12)</td>
<td>10/73 (14)</td>
<td>-2 1.11 0.82</td>
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<td>Briguori44 (total study)</td>
<td>2002</td>
<td>43</td>
<td>36-57</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID, 2 d</td>
<td>1.5</td>
<td>10/91 (11)</td>
<td>6/92 (7)</td>
<td>4 0.59 0.31</td>
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<td></td>
</tr>
<tr>
<td>Durham60</td>
<td>2002</td>
<td>121</td>
<td>46-50</td>
<td>Coronary angiography + PCI</td>
<td>2000 mg BID, 2 d</td>
<td>1.5</td>
<td>19/85 (22)</td>
<td>9/95 (10)</td>
<td>12 0.37 0.04</td>
<td></td>
<td></td>
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<tr>
<td>Fung57</td>
<td>2000</td>
<td>83</td>
<td>33</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID, 2 d</td>
<td>2.4</td>
<td>9/42 (21)</td>
<td>1/41 (2)</td>
<td>19 0.11 0.01</td>
<td></td>
<td></td>
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<tr>
<td>Goldenberg58</td>
<td>2004</td>
<td>80</td>
<td>49-39</td>
<td>Coronary angiography + PCI</td>
<td>400 mg tid, 2 d</td>
<td>2.3</td>
<td>6/45 (13)</td>
<td>8/46 (17)</td>
<td>-4 1.30 0.77</td>
<td></td>
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<tr>
<td>Gomes59</td>
<td>2005</td>
<td>156</td>
<td>52-52</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID, 2 d</td>
<td>1.3</td>
<td>8/79 (10)</td>
<td>8/77 (10)</td>
<td>0 1.03 1.00</td>
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</tr>
<tr>
<td>Kefer60</td>
<td>2003</td>
<td>104</td>
<td>13</td>
<td>Coronary angiography + PCI</td>
<td>IV 1200 mg</td>
<td>1.1</td>
<td>3/51 (6)</td>
<td>2/53 (8)</td>
<td>2 1.56 0.68</td>
<td></td>
<td></td>
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<tr>
<td>Louhinalaikai61</td>
<td>2003</td>
<td>47</td>
<td>NA</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID, 2 d</td>
<td>NA</td>
<td>3/23 (13)</td>
<td>8/24 (33)</td>
<td>-20 1.92 0.33</td>
<td></td>
<td></td>
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<tr>
<td>Ochoa62</td>
<td>2004</td>
<td>80</td>
<td>49-41</td>
<td>Coronary angiography + PCI</td>
<td>1000 mg BID, 2 h</td>
<td>2.0</td>
<td>11/44 (25)</td>
<td>3/36 (8)</td>
<td>17 0.33 0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oldemeyer63</td>
<td>2003</td>
<td>96</td>
<td>49-41</td>
<td>Coronary angiography + PCI</td>
<td>1500 mg BID, 2 d</td>
<td>2.6</td>
<td>3/47 (6)</td>
<td>4/49 (8)</td>
<td>-2 1.28 1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tadros64</td>
<td>2003</td>
<td>110</td>
<td>NA</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID, 2 d</td>
<td>NA</td>
<td>9/55 (16)</td>
<td>3/55 (5)</td>
<td>11 0.13 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vallero65</td>
<td>2002</td>
<td>20</td>
<td>NA</td>
<td>Coronary angiography + PCI</td>
<td>600 mg BID, 2 d</td>
<td>1.5</td>
<td>0/8 (0)</td>
<td>2/12 (17)</td>
<td>-17 NA 0.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Webb66</td>
<td>2004</td>
<td>349</td>
<td>31-39</td>
<td>Coronary angiography + PCI</td>
<td>IV 500 mg immediately before CM</td>
<td>1.6</td>
<td>47/180 (21)</td>
<td>51/169 (23)</td>
<td>-2 1.12 0.55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pt indicates patient; diabetes, patients with diabetes mellitus (%) in placebo group and in acetylcysteine group; ARR, absolute risk reduction; RR, relative risk; PCI, percutaneous coronary intervention; CM, contrast media; and NA, not given. To convert serum creatinine to μmol/L, multiply by 88.4.
Acetylcysteine: Meta-Analyses

Data from several meta-analyses on the effect of acetylcysteine are summarized in Table 3. The first meta-analysis by Birck et al showed that, compared with periprocedural hydration alone, the administration of acetylcysteine significantly reduced the risk of CIN in patients with preexisting renal insufficiency. Isenbarger et al reported a similar result. The meta-analysis by Alonso et al including 8 prospective, randomized trials showed that acetylcysteine significantly reduced CIN. However, these authors further noted a significant heterogeneity in the acetylcysteine effect across trials. The meta-analysis of Kshirsagar et al used unpublished data and data from abstracts and did not report summary data for relative risk and CIs. The meta-analysis by Nallamothu et al included 4 additional studies published as abstracts. The meta-analysis by Pannu et al included 3 additional studies published as abstracts or in press. The meta-analysis by Kshirsagar et al used unpublished data and data from abstracts and did not report summary data for relative risk and CIs. The meta-analysis by Tepel et al on the use of acetylcysteine arose from a nonrandomized study that investigated different markers of renal function without exposure to contrast agents. That study showed that acetylcysteine together with adequate hydration may be useful as standard prophylactic procedure in patients at high risk for CIN.

### Table 3. Meta-Analyses of Randomized, Prospective Trials on Effect of Acetylcysteine for Prevention of CIN

<table>
<thead>
<tr>
<th>First Author and Reference</th>
<th>Year of Publication</th>
<th>No. of Trials Included in Meta-Analysis</th>
<th>References of Trials Included in Meta-Analysis</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birck68</td>
<td>2003</td>
<td>7</td>
<td>44, 47, 49, 52, 53, 54, 56</td>
<td>0.435 (95% CI, 0.215-0.879)</td>
</tr>
<tr>
<td>Isenbarger69</td>
<td>2003</td>
<td>7</td>
<td>44, 47, 49, 52, 53, 54, 56</td>
<td>0.370 (95% CI, 0.160-0.840)</td>
</tr>
<tr>
<td>Alonso70</td>
<td>2004</td>
<td>12</td>
<td>43, 44, 47, 49, 52, 53, 54, 56</td>
<td>0.550 (95% CI, 0.340-0.910)</td>
</tr>
<tr>
<td>Bagshaw71</td>
<td>2004</td>
<td>14</td>
<td>43, 44, 47, 48, 49, 50, 52, 54, 56, 57, 58, 60, 63, 65</td>
<td>0.540 (95% CI, 0.320-0.910)</td>
</tr>
<tr>
<td>Pannu72</td>
<td>2004</td>
<td>15</td>
<td>43, 44, 47, 49, 52, 54, 56, 57, 58, 61, 62, 63, 65</td>
<td>0.650 (95% CI, 0.430-1.000)</td>
</tr>
<tr>
<td>Kshirsagar73</td>
<td>2004</td>
<td>16</td>
<td>42, 44, 47, 49, 52, 53, 54, 56, 57, 58, 61, 62, 63, 65</td>
<td>ND</td>
</tr>
<tr>
<td>Nallamothu74</td>
<td>2004</td>
<td>20</td>
<td>43, 44, 47, 48, 49, 50, 52, 53, 54, 56, 57, 58, 61, 62, 63, 65</td>
<td>0.730 (95% CI, 0.520-1.000)</td>
</tr>
<tr>
<td>Liu75</td>
<td>2005</td>
<td>9</td>
<td>43, 44, 47, 49, 52, 53, 54, 56, 62</td>
<td>0.430 (95% CI, 0.240-0.750)</td>
</tr>
<tr>
<td>Duong76</td>
<td>2005</td>
<td>14</td>
<td>44, 47, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 63, 64</td>
<td>0.570 (95% CI, 0.370-0.840)</td>
</tr>
</tbody>
</table>

ND indicates not determined. First author (reference), year of publication, No. and references of included trial, and relative risk (95% CI) are given for the 9 meta-analyses. The meta-analysis by Alonso et al included 4 additional studies published as abstracts. The meta-analysis by Pannu et al included 3 additional studies published as abstracts or in press. The meta-analysis by Kshirsagar et al used unpublished data and data from abstracts and did not report summary data for relative risk and CIs. The meta-analysis by Nallamothu et al included 4 additional studies published as abstracts.

could not show a beneficial additional effect. What are the reasons for these contradictory results? Many prospective randomized trials used several different procedures, different types and volumes of contrast media, different timing and dosage of acetylcysteine administration, and different routes (intravenous or oral) of administration. The study by Briguori et al emphasized the importance of acetylcysteine dosage. Their study indicated that the administration of a double dose of acetylcysteine (1200 mg twice daily) was superior compared with a standard dose of 600 mg twice daily. Baker et al showed that the intravenous administration of high-dose acetylcysteine was also effective. However, some questions on the use of acetylcysteine arose from a nonrandomized study that investigated different markers of renal function after administration of acetylcysteine to healthy subjects without exposure to contrast agents. That study showed that in healthy subjects acetylcysteine reduced serum creatinine by 3.5%, serum urea by 7.7%, and cystatin C concentrations by 1.3%. These findings may indicate that acetylcysteine may also affect creatinine or urea metabolism.

### Other Drugs and Procedures to Prevent CIN

Other drugs and procedures have been suggested to prevent CIN, including ascorbic acid, theophylline, fenoldopam, calcium antagonists, and periprocedural hemofiltration. Spargias et al showed in a prospective randomized study in patients with preexisting renal insufficiency that CIN occurred in 11 of 118 patients (9%) receiving 7 g ascorbic acid but in 23 of 113 patients (20%) in the control group (relative risk, 0.46; 95% CI, 0.23 to 0.90; P = 0.02). The effect of theophylline on CIN has been investigated in a meta-analysis by Bagshaw and Ghali. They included 9 randomized controlled trials showing evidence of heterogeneity of results across the trials. The overall pooled odds ratio was 0.40 (95% CI, 0.14 to 1.16; P = 0.09), indicating no significant prophylactic effect of theophylline on CIN. In the CONTRAST study, CIN occurred in 46 of 137 patients (34%) receiving the selective dopamine-1 agonist fenoldopam intravenously and in 44 of 146 patients (30%) in the control group (relative risk, 1.11; 95% CI, 0.79 to 1.57; P = 0.61), indicating no preventive effect. Calcium antagonists have been used to prevent CIN; however, most studies did not show a significant prophylactic effect of calcium antagonist on CIN. Current evidence does not support the use of postprocedural hemodialysis for...
prevention of CIN.\textsuperscript{83} However, periprocedural hemofiltra-
tion given in an intensive care unit setting appears to be effective
in preventing CIN (3 of 58 patients [5\%] versus 28 of 56
patients [50\%]; relative risk, 0.10; 95\% CI, 0.03 to 0.32;
P<0.0001) and is associated with improved in-hospital and
long-term outcomes.\textsuperscript{84} However, periprocedural hemofiltra-
tion is an invasive and costly procedure that is not directly
applicable to all high-risk patients who are exposed to
contrast agents for simpler procedures.

Conclusions
In summary, CIN is a common cause of acute renal functional
impairment and accounts for significant morbidity and mor-
tality. Patients with chronic renal failure, diabetes mellitus,
congestive heart failure, older age, hypotension, and anemia
are at particular risk. The primary goal should be to avoid
contrast media to prevent CIN, if at all possible, and risk
factors should be recognized. Prospective, randomized trials
identified significant differences between contrast agents due
to their physicochemical properties, and low-osmolar or
iso-osmolar contrast media should be used to prevent CIN in
at-risk patients. The volume of contrast media should be as
low as possible. Current evidence supports periprocedural
hydration with preferably intravenous administration of 0.9%
isonic saline or an isonionic sodium bicarbonate solution.
There is limited evidence that any pharmaceutical interven-
tion, eg, acetylcysteine, may prevent CIN.

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