

## COMPLICATIONS

### Contrast-Induced Nephropathy

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*Radiological procedures utilizing intravascular iodinated contrast media are being widely applied for both diagnostic and therapeutic purposes and represent one of the main causes of contrast-induced nephropathy (CIN) and hospital-acquired renal failure. Due to the lack of any effective treatment, prevention of this iatrogenic disease, which is associated with significant in-hospital and long-term morbidity and mortality and increased costs, is the key strategy. However, prevention of CIN continues to elude clinicians and is a major concern during percutaneous coronary interventions (PCI), as patients undergoing these procedures often have multiple comorbidities. The purpose of this article is to examine the pathophysiology, risk factors, and clinical course of CIN, as well as the most recent studies dealing with its prevention and potential therapeutic interventions, especially during PCI. (J Interv Cardiol 2008;21:74–85)*

#### Introduction

Contrast-induced nephropathy (CIN), overlooked for many years by health professionals because of an underappreciation of the magnitude and the clinical impact of the problem, has become a widely discussed and debated topic in modern cardiovascular medicine. Currently, CIN is recognized as the third leading cause of hospital-acquired acute renal failure, accounting for 11% of all cases and contributing to prolonged hospital stay and increased medical costs.<sup>1,2</sup> Furthermore, the estimated mortality rate in patients who develop acute deterioration in renal function after intravascular administration of contrast media (CM) may be as high as 35%, and, in survivors, renal function may fail to return to normal in as many as 30%.<sup>3</sup> It is very likely that this clinical problem will assume even greater importance in the years to come. Indeed, due to the aging process, diabetes, or other underlying diseases, an increasing number of patients with some degree of renal impairment will be referred for cardiac catheterization as well as other procedures that use intravas-

cular CM. Notably, the incidence of diabetes—the primary cause of end-stage renal disease—is increasing by 4–5% per year, and the prevalence of end-stage renal disease is expected to rise by 77% over the next decade.<sup>4</sup>

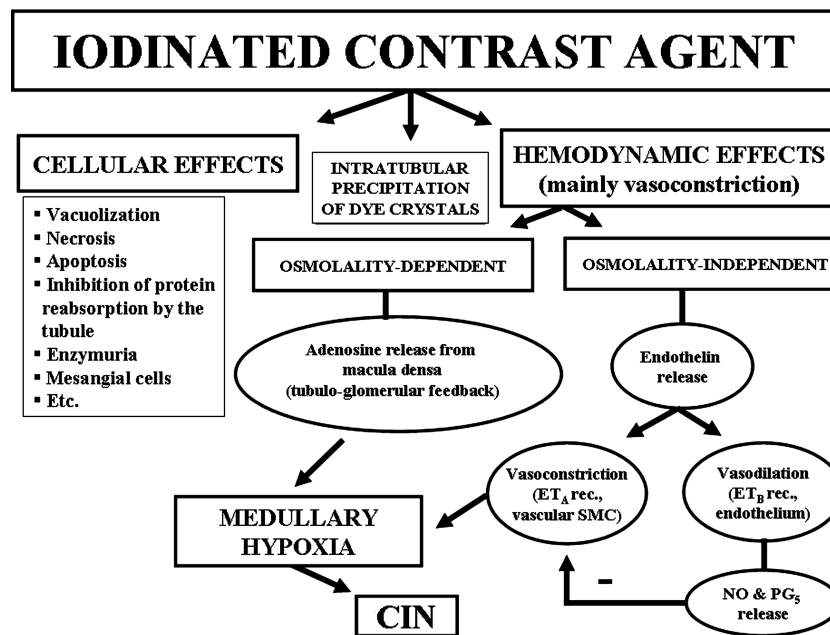
#### Definition

Although there is no universally accepted definition, CIN refers to an absolute increase in serum creatinine of 0.5 mg/dL (44  $\mu$ mol/L), or a relative 25% increase from the baseline value, assessed 48–72 hours following intravascular administration of CM.<sup>5</sup> Based on these definitions, the overall incidence of CIN in the general population is estimated to be lower than 3%, but it can rise up to 50% or more in patients with multiple risk factors. However, the reported frequencies probably underrepresent the magnitude of the problem, because serum creatinine is not measured routinely following CM exposure.

#### Pathophysiology

Although the exact mechanism of CIN has not been completely elucidated, there is increased evidence that

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**Figure 1.** The postulated mechanisms intertwined in the pathophysiology of contrast-induced nephropathy (CIN). ET<sub>A</sub> = endothelin A; ET<sub>B</sub> = endothelin B; SMC = smooth muscle cells; NO = nitric oxide; and PG<sub>5</sub> = Prostaglandin 5.

a combination of direct toxic effects on tubular epithelial cells and renal ischemia play a pathogenetic role<sup>6</sup> (Fig. 1). Direct toxic effects in the proximal convoluted tubular cells and in the inner cortex of the kidneys have been demonstrated following exposure to CM. Injury due to enhanced production of oxygen-free radicals and lipid peroxidation of biological membranes may also be implicated. Concerning ischemic injury, studies have shown that immediate vasoconstriction and reduction in renal blood flow after CM administration are not uniform and that CM appear to exert regional effects within the kidney, with increases in blood flow to the renal cortex and simultaneous flow reduction to the outer medulla. The deeper portion of the outer medulla of the kidney is particularly vulnerable to ischemic injury. This area is maintained to low oxygen tension, with  $pO_2$  levels often as low as 20 mmHg, whereas its metabolic activity and oxygen requirements are high.

Two possible mechanisms by which medullary hypoxia and ischemia may occur in response to CM exposure have been proposed. First, CM may cause renal vasoconstriction, and both increased activity of several intrarenal mediators (adenosin, vasopressin, angiotensin II, dopamine-1, and endothelin) and decreased activity of renal vasodilators (nitric oxide and

prostaglandins). Second, CM may decrease renal blood flow indirectly by causing erythrocyte aggregation.

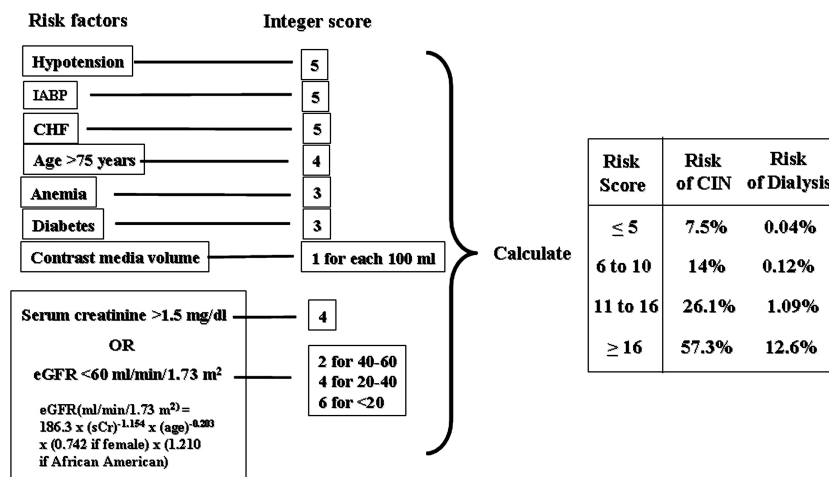
### Risk Factors and Risk Stratification

A large body of data indicates that the risk of CIN is related to patient characteristics, clinical setting, and other modifiable factors (Table 1). Evidence provided

**Table 1.** Risk Factor for Contrast-Induced Nephropathy

| Patient-Related Factors                      | Procedure-Related Factors                     |
|----------------------------------------------|-----------------------------------------------|
| CKD                                          | Large volume of CM                            |
| CHF (low cardiac output)                     | Intraarterial CM administration               |
| Diabetes mellitus with CRF                   | Multiple administration of CM within 72 hours |
| Age                                          | Osmolality and ionicity of CM                 |
| Intravascular volume depletion (dehydration) | IABP                                          |
| Systemic hypotension                         | Emergent/primary PCI                          |
| Nephrotoxic drugs                            |                                               |
| Anemia, PCI-related blood loss               |                                               |
| Renal transplant                             |                                               |
| Hypoalbuminemia (<35 g/L)                    |                                               |

CKD = chronic kidney disease; CHF = chronic heart failure; PCI = percutaneous coronary interventions; CM = contrast media; IABP = intraaortic balloon pump.



**Figure 2.** Risk prediction scheme for the development of contrast-induced nephropathy (CIN) and for serious renal failure requiring dialysis. Anemia: baseline hematocrit value <39% for men and <36% for women; CHF: congestive heart failure functional class III/IV, and/or history of pulmonary edema; eGFR: estimated glomerular filtration rate; hypotension: systolic blood pressure <80 mmHg for at least 1 hour requiring inotropic support with medications or intraaortic balloon pump (IABP) within 24 hours periprocedurally. From Mehran et al.<sup>9</sup>

from clinical studies indicates that renal impairment has a strong and consistent association with CIN development. The higher the baseline creatinine value, the greater is the risk of CIN.<sup>7</sup> The presence of diabetes mellitus may significantly increase the risk in patients with preexisting renal dysfunction. Studies have shown that these patients have a fourfold higher rate of CIN as compared to those without diabetes or renal impairment.<sup>8</sup> However, it is not clear whether the risk of CIN is significantly increased in patients with diabetes who do not have renal impairment. Additional risk factors include older age, likely in relation to the decline in renal function with aging congestive heart failure, reduced effective arterial volume, as in case of dehydration, nephrosis, and cirrhosis, type and volume of CM, anemia and procedure-related blood loss, concurrent use of potentially nephrotoxic drugs, such as diuretics, and aminoglycosides, as well as drugs impairing the renovascular autoregulation such as nonsteroidal anti-inflammatory drugs.<sup>8,9</sup>

Apart from the known unfavorable association of diabetes and renal insufficiency, the presence of two or more risk factors is additive, possibly by a variety of interacting mechanisms, and the likelihood of CIN rises sharply as number of risk factors increases. Information derived from multiple large-scale studies has led to the development of multivariate prediction scoring schemes for patients undergoing percutaneous coronary interventions (PCI)<sup>8-12</sup> (Fig. 2). Application

of these risk scores showed that patients with multiple risk factors have a very high, if not certain, expectation for CIN development after contrast exposure. It should be noted, however, that these risk scores have been evaluated retrospectively, and none of them has been prospectively validated in different populations. Thus, a current recommendation for the clinical use of risk scoring based on these data cannot be made.

### Clinical Presentation and Prognostic Implications

The clinical course of CIN is usually characterized by serum creatinine rise within 24 hours after administration of CM, typically peaking on the second or third day.<sup>5</sup> Usually, serum creatinine returns to baseline value within 7–10 days. Although the clinical relevance of CIN may not be immediately evident given the subclinical course and the high frequency of recovery of renal function, some degree of residual renal impairment has been reported in as many as 30% of those affected and up to 7% of patients may require temporary dialysis or progress to end-stage renal failure.<sup>6</sup> Serious clinical consequences, including death, may occur in patients developing CIN. Patients with CIN were observed to have several noncardiac in-hospital complications, including hematoma formation, pseudoaneurysms, stroke, coma, adult respiratory

distress syndrome, pulmonary embolism, and gastrointestinal hemorrhage.<sup>13</sup> Patients who develop CIN after PCI have a 15-fold higher rate of major adverse cardiac events during hospitalization than patients without this complication.<sup>13</sup> They also have a 6-fold increase in myocardial infarction and an 11-fold increase in coronary vessel reocclusion.<sup>12</sup> Although few patients with CIN require dialysis (<1%), the latter have a more complicated clinical outcome than those who do not require renal replacement therapy, including a significantly higher rate of non-Q-wave myocardial infarction (46% vs. 15%), pulmonary edema (65% vs. 3%), and gastro-intestinal bleeding (16% vs. 1%). Moreover, they have a 15-fold longer stay in the intensive care unit and a 5-fold longer in-hospital stay.<sup>2,14</sup>

Patients undergoing primary PCI are a particularly high-risk group. In one series, major in-hospital complications, including acute pulmonary edema, respiratory failure, and cardiogenic shock, were significantly more common in patients developing CIN. A higher mortality rate was also documented for patients developing CIN compared with those without CIN (31% vs. 0.6%;  $P = 0.0001$ ).<sup>15</sup>

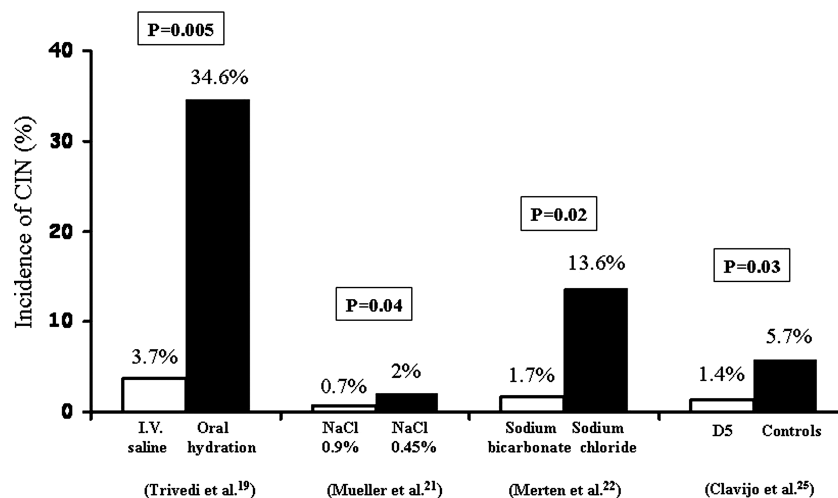
## Prophylactic Measures

**Fluid Administration.** Hydration remains the cornerstone for the prevention of CIN, even though no randomized controlled trial comparing a strategy of volume expansion with no volume expansion has been performed. Hydration results in plasma volume expansion with concomitant suppression of the renin-angiotensin-aldosterone system, down-regulation of the tubuloglomerular feedback, dilution of the CM—and thus prevention of renal cortical vasoconstriction—and avoidance of tubular obstruction.<sup>16</sup> Multiple trials have addressed type, amount, duration, and route of fluid administration to prevent CIN.<sup>17–20</sup> However, many of these aspects remain undefined. Trivedi et al.<sup>19</sup> found that oral hydration alone appeared to be inferior to intravenous hydration with respect to the development of CIN. By comparing patients treated with hydration and mannitol and hydration and furosemide, Solomon et al.<sup>17</sup> demonstrated that intravenous infusion of 0.45% saline (1 mL/kg/hour), starting 4–6 hours before CM administration, and continued for 24 hours afterward, reduced the risk of CIN in patients with mild renal insufficiency undergoing cardiac angiography. More recent evidence suggests that hydration

with isotonic saline is superior to half-isotonic saline, likely because of the enhanced ability of isotonic fluids to expand intravascular volume.<sup>21</sup> The advantage of isotonic hydration is certainly demonstrated in patients with normal renal function and with a low risk of CIN, but these results cannot be transferred conclusively to patients with moderate and severe chronic renal failure. Recently, Merten et al.<sup>22</sup> demonstrated that hydration with sodium bicarbonate (154 mEq/L of sodium bicarbonate in dextrose and water at a rate of 3 mL/kg/hour per 1 hour before CM exposure, followed by 1 mL/kg/hour during, and for 6 hours after the procedure) is more effective than hydration with sodium chloride and may provide additional renoprotection by alkalinizing renal tubular fluid and thereby minimizing tubular damage. The authors postulated that the effects of bicarbonate on urine pH may reduce oxygen-free radical formation, thereby reducing contrast-induced injury. Two recent studies further support the use of bicarbonate for prevention of CIN.<sup>23,24</sup> Finally, Clavijo et al.<sup>25</sup> have most recently reported a retrospective analysis showing that a rapid intraarterial infusion of dextrose 5% (1 L administered through the femoral artery sheath as a bolus >5 minutes immediately before angiography) was well tolerated and effective against CIN in patients with a creatinine clearance  $\leq 60$  mL/min (Fig. 3).

Although a clearly emerging concept is that volume expansion is critical in the prevention of CIN, the prognostic impact of hydration is still controversial, and we have no definite information on the possible advantage of this strategy on CIN-associated cardiovascular complications and mortality rate in high-risk patients. We also lack data from controlled clinical trials that define the most effective hydration period, infusion rate, or hydration volume. Additional studies are also required to investigate the role of hydration in patients with congestive heart failure and renal insufficiency, a population that has always been poorly represented in previous studies, and in which vigorous hydration is logistically difficult, and poorly tolerated.

**Pharmacologic Prevention Strategies.** Several pharmacologic approaches have been devised to mitigate the risk of CIN in patients with preexisting renal disease<sup>26</sup> (Table 2). A number of studies have targeted renal vasoconstriction and hypoxia-induced oxidative stress, which are among the mechanisms by which CM are believed to cause nephrotoxicity, and have evaluated the role of pharmacologic adjunct therapies designed to counteract them. However, with the exception



**Figure 3.** Studies comparing different hydration protocols for the prevention of contrast-induced nephropathy (CIN). In the Trivedi et al.,<sup>19</sup> Mueller et al.,<sup>21</sup> and Clavijo et al.<sup>25</sup> studies, CIN was defined as an increase of 0.5 mg/dL or more in serum creatinine within 48 hours. In the Merten et al.<sup>22</sup> study, it was defined as an increase of 25% or more. I.V. = intravenous; NaCl = sodium chloride; and D5 = 5% dextrose.

of volume expansion and antioxidant agents, few of these adjunctive therapies have shown any clear and consistent benefit.

*Drugs – vasodilators.*

1. *Endothelin receptor antagonist:* Due to the potential role of hemodynamic effects induced by

**Table 2.** Pharmacologic Strategies Evaluated for Contrast-Induced Nephropathy Risk Reduction

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

CM, numerous vasodilator drugs have been tested for prevention of acute reduction in renal function. The possible role of endothelin-induced renal vasoconstriction has led to the evaluation of a nonselective endothelin receptor antagonist in a multicenter, double-blind randomized trial of high-risk patients undergoing coronary angiography.<sup>27</sup> Compared with those randomized to placebo, a significantly higher percentage of patients who received active therapy developed CIN (56% vs. 29%;  $P = 0.002$ ). However, this study evaluated a mixed endothelin A and B receptor antagonist, and this disappointing result may tentatively be explained by endothelin B receptor inhibition, which favors vasoconstriction. To date, it is not known whether selective endothelin A blockade may be beneficial in preventing CIN.

2. *Atrial natriuretic peptide:* No benefit was observed with the intravenous administration of this agent in a large multicenter, prospective, double-blind, placebo-controlled randomized trial.<sup>28</sup>
3. *Calcium channel blockers:* Verapamil, diltiazem, and amlodipine have been found to attenuate the renal vasoconstrictor response to CM, and to inhibit CIN in rats. A randomized placebo-controlled study of 35 patients with renal insufficiency has shown that oral nitrendipine (20 mg/day for 3 days) is effective for preventing the decrease in glomerular filtration

rate.<sup>29</sup> In contrast, other studies with nitrendipine, felodipine, and amlodipine did not confirm the beneficial effects of calcium antagonists for prevention of CIN. However, it must be emphasized that only dihydropyridine calcium channel blockers have been clinically tested so far. These agents have a more potent peripheral vasodilating effect than verapamil or diltiazem. Therefore, a possible protective renal effect from calcium channel inhibition, which leads to lower renal perfusion pressure, may be offset by the hypotensive effect caused by these drugs. Current recommendations do not include calcium channel blockers for the prevention of CIN.

4. *Prostaglandins*: Prostaglandin E<sub>1</sub> (PGE) has been considered promising as a prophylactic agent against CIN due to its vasodilatory effects. A recent randomized, placebo-controlled pilot study suggests that prophylactic administration of iloprost, a prostacyclin (PGI<sub>2</sub>) analogue, at a dose of 1 ng/kg/min, in patients with chronic renal failure undergoing a coronary procedure is safe and may effectively prevent CIN.<sup>30</sup> Further studies are needed to confirm the effectiveness of this agent.
5. *Adenosine antagonists*: Contrast media stimulate the intrarenal secretion of adenosine, which binds to the renal adenosine receptor and acts as a potent vasoconstrictor, primarily in the efferent arterioles, reducing renal blood flow. As this vasoconstrictive response can be blunted with theophylline in experimental animals, multiple investigators have evaluated aminophylline and theophylline as a potential means of reducing the risk of CIN in human subjects. However, these studies have been limited by a small sample size, variation in timing and dosage of drug administration, and variation in the definition of CIN. Although a meta-analysis of seven trials including 480 patients suggested a beneficial effect of theophylline,<sup>31</sup> further studies should be performed to definitively determine its efficacy, safety, and utility. In particular, the potential benefits of theophylline must be weighed against potential side effects.<sup>32</sup>
6. *Dopamine*: Although theoretically justified, studies testing the effectiveness of low (<2 µg/kg/min) doses of dopamine have shown negative or neutral results.<sup>33,34</sup> This may be due to hypovolemia and tachyarrhythmia induced by the

diuretic and pro-arrhythmogenic effects of this drug, both leading to reduced cardiac output and reduced effective circulating arterial volume.

7. *Fenoldopam*: In contrast to dopamine, fenoldopam is a selective dopamine-1 receptor agonist with systemic and renal arteriolar vasodilatory properties that does not stimulate dopamine-2 or adrenergic receptors, even when administered at higher doses. Thus, fenoldopam significantly increases renal blood flow and decreases renal vascular resistance, without altering glomerular filtration rate.<sup>35</sup> Following preliminary studies showing a benefit in reducing CIN, a more recent prospective, randomized trial (CONTRAST trial), evaluating fenoldopam in 315 patients at risk for developing CIN undergoing diagnostic and/or interventional cardiology procedures, has shown negative results.<sup>36</sup>
8. *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 CIN in patients with mild-to-moderate renal failure included in a randomized, placebo-controlled trial.<sup>37</sup>
9. *Angiotensin-converting enzyme inhibitors*: The role of angiotensin-converting enzyme inhibitors for the prevention of CIN is still controversial. Preliminary studies suggest that abnormalities of renal perfusion, possibly mediated by the renin angiotensin system, are responsible for the development of CIN, and administration of captopril may offer protection against its development, particularly in diabetic patients.<sup>38</sup>

#### *Drugs – antioxidants.*

1. *N-Acetylcysteine*: N-acetylcysteine (NAC), the most widely studied of all prophylaxis strategies, has direct vasodilating effects on kidney vessels, contributing to improved renal hemodynamics.<sup>39</sup> It may also attenuate endothelial dysfunction, and, more notably, it is able to scavenge oxygen-free radicals, thus preventing direct oxidative tissue damage occurring in patients receiving CM. Tepel et al.<sup>40</sup> first reported that NAC (600 mg orally twice daily) plus hydration before and after CM administration offers protection against CIN in patients with renal insufficiency undergoing computed tomography with a constant dose

(75 mL) of CM (2% vs. 21%;  $P = 0.01$ ). This finding was supported by some, but not all, subsequent clinical trials investigating the efficacy of NAC in preventing CIN, both in patients with preexisting renal insufficiency and in those with normal renal function.<sup>41–44</sup>

Several meta-analyses have been published on this topic to date.<sup>45–55</sup> By combining the data from available prospective controlled clinical trials, an overall significant relative risk reduction in chronic renal failure patients given NAC was demonstrated.<sup>56</sup> Nine have presented pooled risk estimates suggesting benefit. However, as the literature currently available is greatly heterogeneous, the benefit of oral NAC among all individuals with renal insufficiency cannot be clearly confirmed.<sup>48</sup> Differences in CM type and volumes, definitions of CIN, patient selection, type of intervention, applied hydration regimens, NAC dose (cumulative dosage varied between 1,500 and 6,000 mg), and route of administration (intravenous vs. oral), as well as the timing of the procedure (urgent vs. elective), may have contributed to the heterogeneity observed in the pooled analysis. Some recent studies utilizing a greater dose of NAC seem to support the hypothesis of a dose-dependent protective effect of NAC.<sup>57–59</sup> Moreover, two very recent randomized trials demonstrated an improved preventive effect against CIN when two different antioxidant strategies, such as NAC and bicarbonate, were combined.<sup>23,24</sup> This seems to confirm the relevant pathogenetic role of oxidative stress in CIN development. A article by Hoffman et al.<sup>60</sup> suggested that NAC has a direct effect on the tubular handling of creatinine, but not on cystatin C, in healthy volunteers. Therefore, this surrogate marker of glomerular filtration should be prudentially used, and the protective effect of this drug should not be overstated. This, however, has never been demonstrated in patients with chronic renal insufficiency or in the setting of acute renal failure. In a recent experimental study in which serum creatinine and cystatin C were evaluated after NAC administration, the two markers showed a similar pattern, indicating no influence of NAC on serum creatinine levels.<sup>61</sup> Similarly, no difference in serum creatinine and cystatin C response to NAC was observed by Haase et al.,<sup>62</sup> in patients undergoing cardiac surgery.

2. *Ascorbic acid*: Additional evidence of the effectiveness of an antioxidant strategy comes from the recent observation by Spargias et al.,<sup>63</sup> who investigated the impact of ascorbic acid in a randomized, double-blind, placebo-controlled trial including 231 patients with a serum creatinine concentration  $\geq 1.2$  mg/dL who underwent coronary angiography and/or intervention. Ascorbic acid (3 g at least 2 hours before the procedure and 2 g in the night and the morning after the procedure) or placebo were administered orally. CIN occurred in 9% of the ascorbic acid group and in 20% of the placebo group ( $P = 0.02$ ). The antioxidant ascorbic acid has been shown to attenuate renal damage caused by a variety of insults, such as postischemic stress, cisplatin, aminoglycosides, and potassium bromate in animals. When added to NAC, however, ascorbic acid did not show any improvement as compared to NAC alone.<sup>23</sup> Thus, the possible benefits of ascorbic acid deserve further investigation.
3. *Trimezatidine*: This drug has been initially described as a cellular antiischemic agent. Further studies, however, demonstrated that trimezatidine exerts potent antioxidant activity in myocardial, renal, and hepatic ischemia-reperfusion injury. In a recent randomized, controlled trial, trimezatidine (20 mg t.i.d. orally for 72 hours starting 48 hours before the procedure) in addition to standard intravenous saline hydration was compared with hydration alone in 82 patients with mild chronic renal insufficiency undergoing elective coronary procedures.<sup>64</sup> The incidence of CIN was significantly lower in patients receiving trimezatidine (2.5% vs. 16.6%;  $P < 0.05$ ). The potential usefulness of this drug in the prevention of CIN, particularly in higher risk patients, should be investigated in larger prospective clinical studies.

#### *Other drugs.*

1. *Statins*: It has been suggested that statins may reduce CIN by means of their beneficial effects on endothelial function and oxidative stress. A retrospective review of 1,002 patients with renal insufficiency undergoing coronary angiography suggested that the risk of CIN was lower in patients in whom a statin was initiated just before the procedure.<sup>65</sup> The results of a large PCI registry study including 29,409 patients also

confirmed this conclusion.<sup>66</sup> Nevertheless, to date, there is not enough evidence to support the use of statins before radiological procedures in patients in whom these drugs are not otherwise indicated.

**Renal Replacement Therapies. Hemodialysis.** On the basis of studies demonstrating its effectiveness in CM removal, hemodialysis (HD) has been proposed as a CIN preventive strategy after radiographic procedures. However, several studies have shown that the strategy of performing HD immediately after administration of CM in patients with reduced renal function does not prevent CIN.<sup>67–70</sup> The incongruence between the effective removal of CM by HD and the lack of a preventive effect against CIN may be the result of HD-related nephrotoxicity, caused by activation of inflammatory reactions, coagulation processes, and release of vasoactive substances that may induce acute hypotension.<sup>71</sup> Furthermore, hemodynamic instability due to the osmotic shift of fluid from the intravascular to the interstitial and intracellular compartments, and to the dialysis-associated ultrafiltration, is frequently observed during HD. Hypovolemia can induce renal hypoperfusion, vasoconstriction, and ischemic injury. A third possible reason may be that renal injury may occur rapidly after administration of CM before HD is started. Indeed, in most of the studies, CM removal by HD was started after a relatively long time, even hours, after the initial injection of the agent, whereas renal hypoperfusion has been demonstrated within 20 minutes after the injection of CM, suggesting that the renal insult may occur at its first renal hemodynamic passage. Thus, the explanation for the lack of clinical benefit could be a too long delay between exposure to and elimination of CM. However, the hypothesis that a simultaneous HD therapy may protect the patient from CIN could not be demonstrated, presumably because plasma peak concentration of CM was not affected by this type of therapy. Indeed, the peak value of CM concentration, more than the time to which kidneys are exposed to it, is thought to be the major factor responsible for CIN.

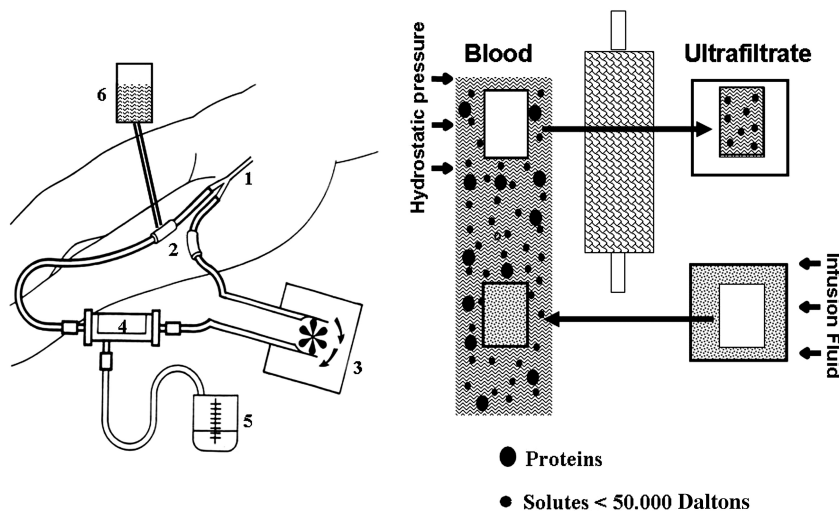
**Hemofiltration.** Hemofiltration (HF) is a simple renal replacement therapy that can be easily performed by personnel without specific nephrologic experience and that permits effective fluid and solute removal with greater fluid volume control and hemodynamic stability than HD (Fig. 4). The better hemodynamic stability represents a clear advantage of HF over HD, es-

pecially in the treatment of patients with associated acute renal and cardiac insufficiency. A randomized study from our institute provided evidence that HF offers protection against CIN in high-risk patients.<sup>72</sup> CIN occurred in only 5% of patients in the HF group, and in 50% of patients in the control group ( $P < 0.001$ ). Moreover, the in-hospital and 1-year mortality rates were significantly reduced in patients treated with HF when compared to the control group (2% vs. 18% and 10% vs. 30%, respectively). The mechanisms involved in the prophylactic effect of HF remain unclear. Positive effects may derive from its ability to remove CM from the circulation, thereby reducing kidney exposure to its nephrotoxic effects. However, this hypothesis is questioned by the results of a recent randomized clinical study, in which two different HF protocols for the prevention of CIN in patients with severe renal insufficiency (creatinine clearance  $<30$  mL/min), scheduled for elective cardiovascular procedures, were compared.<sup>73</sup> One group was treated with HF for 18 to 24 hours after the procedure (post-HF group), while another group underwent HF for 6 hours before, and for 18 to 24 hours after, contrast administration (pre/post-HF group). Twenty-six percent of patients in the post-HF group experienced CIN, as compared with only 3% of the pre/post-HF group ( $P = 0.0013$ ). This study confirmed that HF is particularly effective in preventing CIN and the associated poor outcome in high-risk patients. It also demonstrated that a preprocedural session is necessarily required in order to obtain the full clinical benefit of this treatment.

**Type of Contrast Medium.** The use of nonionic low-osmolar CM (LOCM) (600–850 mOsm/kg) has been associated with fewer renal adverse effects than high-osmolar CM (HOCM) (1500–1880 mOsm/kg). A large meta-analysis performed by Barrett and Carlyle pooled data from 31 trials<sup>74</sup> and showed in patients with preexisting CKD, to whom CM was administered intraarterially, a significant reduction of CIN with LOCM. In contrast, no benefit was found among patients with normal renal function, with or without diabetes, and in those receiving CM intravenously. These results were confirmed by Rudnick et al.<sup>75</sup> in a large prospective study of 1,196 patients. They found a significant benefit of LOCM (iohexol) over HOCM (diatrizoate) only in patients with preexisting CKD.

A reduced nephrotoxic effect may be obtained with nonionic iso-osmolar CM (IOCM), as recently demonstrated by the NEPHRIC trial.<sup>76</sup> This was a randomized, double-blind, prospective, multicenter study





**Figure 4.** (Left-hand panel): Graphic representation of the extracorporeal circuit used for hemofiltration. (Right-hand panel): In hemofiltration, blood runs under pressure into the capillaries of the hemofilter. Water and small solutes pass across the capillary membrane by convection. The filtrate is discarded and a solution, in which the major components are at physiologic level, is infused. If there is no need for fluid removal, the rate of fluid replacement is matched with the hemofiltration rate, whereas if there is need to remove fluid, less replacement fluid is infused. 1 = femoral-vein, double-lumen Y cannula; 2 = veno-venous circuit; 3 = blood pump; 4 = hemofilter; 5 = graduate filtrate collector; and 6 = replacement fluid.

comparing the nonionic IOCM iodixanol (290 mOsm/kg) with the nonionic LOCM iohexol. The study included 129 patients with diabetes and creatinine  $\geq 1.5$  mg/dL undergoing coronary or peripheral angiography. There were no differences in baseline creatinine (1.49 vs. 1.6 mg/dL) and CM volume (163 vs. 162 mL) between patients receiving iodixanol or iohexol. The incidence of CIN was 3% in the iodixanol group and 26% in the iohexol group ( $P = 0.002$ ). These results may be explained by the greater osmotic diuresis induced by LOCM, which may increase the work of the medullary tubules and induce ischemia within the renal medulla and volume depletion with activation of

vasoregulatory hormones. Although the results of this study are encouraging, some issues still exist in regards to the superiority of IOCM over LOCM. First, other studies with iodixanol in CKD patients have shown a higher incidence of CIN than that observed in the NEPHRIC study (21% in the RAPID trial, 12% in the study of Boccalandro et al., 33% and 25% with iodixanol and other CM, respectively, in the CONTRAST trial).<sup>36,57,77</sup> Second, in a randomized study by Chalmers and Jackson,<sup>78</sup> the renal tolerance of iodixanol and iohexol was compared in patients with CKD (creatinine  $> 1.7$  mg/dL) who underwent peripheral angiography. More patients in the iohexol group

**Table 3.** Head-to-Head Prospective Randomized Trials Comparing Iso-Osmolar to Low-Osmolar Contrast Agents in High-Risk Patients

| Author                 | Pts (n) | Low Osmolality | Iso-Osmolality | Condition                              | Statistical Result              |
|------------------------|---------|----------------|----------------|----------------------------------------|---------------------------------|
| Aspelin <sup>76</sup>  | 129     | Iohexol        | Iodixanol      | Coronary, CKD (SCr 1.5), 100% DM       | Indixanol superior to iohexol   |
| Chalmer <sup>78</sup>  | 102     | Iohexol        | Iodixanol      | Coronary, CKD (SCr 3.1), 35% DM        | No difference                   |
| Solomon <sup>79</sup>  | 414     | Iopamidol      | Iodixanol      | Coronary, CKD (SCr 1.45), 41% DM       | No difference                   |
| Feldkamp <sup>80</sup> | 221     | Iopromide      | Iodixanol      | Coronary, (CrCl $> 50$ ml/min), 40% DM | No difference                   |
| Ni <sup>81</sup>       | 285     | Iopamidol      | Iodixanol      | Coronary, 47% CKD, 19% DM              | No difference                   |
| Barrett <sup>82</sup>  | 153     | Iopamidol      | Iodixanol      | MDCT, CKD (SCr 1.6), 24% DM            | No difference                   |
| Jo <sup>83</sup>       | 275     | Ioxaglate      | Iodixanol      | Coronary, CKD (SCr 1.34), 48% DM       | Iodixanol superior to ioxaglate |

CrCl = creatinine clearance; CKD = chronic kidney disease; DM = diabetes mellitus; MDCT = multidetector computed tomography; and SCr = serum creatinine.

experienced an increase in creatinine  $> 10\%$  (a CIN criterion used only in this study), while the two groups did not differ significantly when the  $>25\%$  creatinine increase criterion was used. According to this study, the difference between the two CM was small and of minor clinical significance. Third, the CARE trial, a recent randomized double-blind study, failed to show any statistical difference after the intraarterial administration of iopamidol or iodixanol to high-risk patients, with or without diabetes mellitus.<sup>79</sup> Similar results were found when iodixanol was compared with another LOCM, iopromide, in low-risk patients.<sup>80</sup>

In summary, the available data do not provide clear evidence to support the theory that IOCM offer an improvement over the LOCM class (Table 3).

## Conclusion

The incidence of CIN is growing largely due to the increasingly frequent use of CM for diagnostic and interventional procedures in patients who are older and have associated comorbidities such as diabetes, cardiac failure, and renal insufficiency. Because CIN is potentially preventable, risk prediction and prophylactic measures are mandatory. Prevention of CIN can be achieved with hydration, use of LOCM or IOCM, limiting CM volume, and stopping nephrotoxic drugs. Despite a large number of studies, most of the prophylactic pharmacologic agents that were evaluated have not proven to be effective. Promising approaches include use of vigorous intravenous hydration with isotonic bicarbonate solution, treatment with NAC at doses commensurate to the contrast media volume, and, in patients with severe renal failure, periprocedural hemofiltration.

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