

Pharmacologic Agents for Prevention of Contrast-Induced Nephropathy

Experts provide their review of the medical options available to reduce CIN after PCI.

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Renal function impairment after exposure to iodine-containing contrast agents is a serious iatrogenic pathologic condition, known as contrast-induced nephropathy (CIN). Per definition, CIN is an absolute (≥ 0.5 mg/dL) or relative ($\geq 25\%$) increase in serum creatinine after exposure to a contrast agent compared to the baseline value, when alternative explanations for renal impairment have been excluded. CIN typically develops within 24 to 96 hours after exposure, with renal function returning to baseline or near-baseline levels in 1 to 3 weeks.¹ The overall incidence of CIN in the general population after receiving iodinated contrast is estimated at 1.2% to 1.6%.^{2,3} In select subsets, however, such as patients with underlying cardiovascular disease, the incidence of CIN is much higher. Chronic renal insufficiency, diabetes mellitus, older age, anemia, and higher volume of contrast media are the most meaningful predictors of CIN.^{4,5} To reliably assess the risk of CIN, we recommend using a simple risk score (Figure 1) that may be quickly calculated based on readily available information.⁵ Today, CIN is one of the most common sources of acute renal failure among hospitalized patients. It is associated with prolonged in-hospital stay and increased morbidity, mortality, and costs.⁶

The unfavorable prognostic implications of CIN make its prevention of paramount importance.^{7,8} In a retrospective analysis of 16,248 patients exposed to contrast media, in-hospital mortality rates were almost fivefold higher in patients that developed CIN (34%) compared with those without renal failure (7%).⁸ Prognosis is especially unfavorable in patients with pre-existing renal disease, in whom contrast material causes further deterioration of renal function and those who require dialysis treatment.^{7,8} In-hospital mortality rates in these subsets were 14.9% and 27.5%, respectively, versus 4.9% in patients with preserved renal

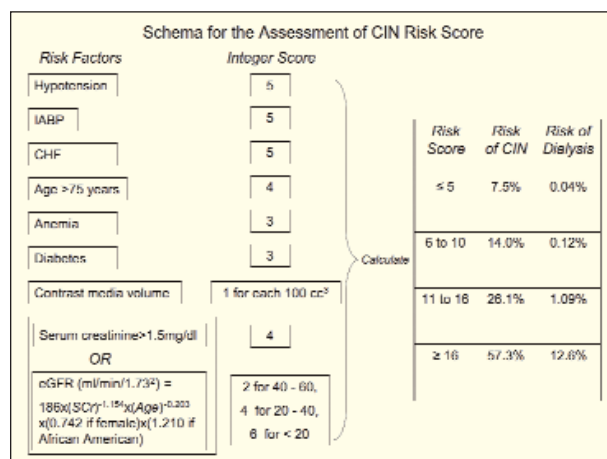


Figure 1. Scheme to define CIN risk score. CHF denotes congestive heart failure class III–IV by New York Heart Association classification and/or history of pulmonary edema. Anemia: baseline hematocrit value <39% for men and <36% for women. Hypotension: systolic blood pressure <80 mm Hg for at least 1 hour requiring inotropic support with medications or an intra-aortic balloon pump within 24 hours periprocedurally. (Adapted and reprinted with permission from Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol*. 2004;44:1393-1399.) eGFR=estimated glomerular filtration rate.

function.^{7,8} Multiple preventive modalities have been investigated and are summarized in Table 1.

HYDRATION

The goal of hydration in patients undergoing contrast

TABLE 1. STUDIES ASSESSING VARIOUS TREATMENT MODALITIES IN THE PREVENTION OF CIN

Treatment Modality	Supports Use	No Effect/Deleterious Effect
Hydration with 0.9% sodium chloride	Solomon et al ⁹	–
Hydration with sodium bicarbonate	Merten et al ¹⁴ Briguori et al ¹⁵	–
N-acetyl-L-cysteine	Tepel et al ¹⁶ Diaz-Sandoval et al ¹⁷ Misra et al ^{20*} Alonso et al ^{21*}	Briguori et al ¹⁸ Webb et al ¹⁹ Bagshaw et al ^{22*} Kshirsagar et al ^{23*} Moore et al ²⁴
Dopamine	Kapoor et al ²⁵	Hans et al ²⁷ Abizaid et al ²⁸
Fenoldopam	Tumlin et al ³⁰	Stone et al ³²
Theophylline	Huber et al ³⁵ Kolonko et al ³⁶ Ix et al ^{39*} Bagshaw et al ^{40*}	Erley et al ³⁷ Shammas et al ³⁸ Abizaid et al ²⁸
Statins	Attallah et al ⁴⁶ Khanal al ⁴⁷	–
Atrial natriuretic peptide	–	Kurnik et al ⁴⁴
Calcium-channel blockers	Neumayer et al ⁴¹	Carraro et al ⁴² Khoury et al ⁴³
Prostaglandin E1	Sketch et al ⁴⁵	–
Hemodialysis	Lee et al ⁵¹	Vogt et al ⁴⁸ Lehnert et al ⁴⁹ Berger et al ⁵⁰
Hemofiltration	Marenzi et al ⁵²	–

*Meta-analysis.

exposure is to establish brisk diuresis before dye administration and to avoid hypotension. The positive effect of adequate hydration in reducing rates of CIN was first established in a randomized study by Solomon et al; among a total of 78 patients with chronic renal insufficiency undergoing angiography, hydration with 0.45% saline (1 mL/kg per hour for 12 hours before and after the procedure; n=28 patients) provided better protection against renal function deterioration than hydration with 0.45% saline plus mannitol (n=25 patients) or furosemide (n=25 patients; $P=.02$ for saline vs saline plus furosemide group).⁹ Another randomized study demonstrated that in patients with mild-to-moderate renal insufficiency, different modes of fluid administration (intravenous vs oral) had similar renoprotective effects.¹⁰ In the randomized, open-label study by Mueller et al comparing two hydration regimens in a total of 1,620 patients undergoing percutaneous coronary intervention (PCI), there was evidence of superiority of isotonic versus half-isotonic saline in reducing rates of CIN (0.7% vs 2%, respectively).¹¹ The benefit of isotonic saline was especially

prominent in women and diabetics and in patients who received more than 250 mL of contrast media.¹¹

In the randomized PRINCE trial, the high urine flow rate achieved with forced diuresis via intravenous crystalloid, mannitol, and furosemide showed only a modest benefit in preventing CIN compared with control (crystalloid plus placebo).¹²

In a single-center study, a strategy of rapid intra-arterial administration of 1,000 mL of 5% dextrose immediately before catheterization was shown to be associated with a lower rate of CIN compared with conventional intravenous hydration in 976 high-risk patients (creatinine clearance, ≤ 60 mL/min; 1.4% vs 5.7%, respectively; $P=.03$).¹³ The data should be further confirmed in larger randomized, multi-center studies.

It should be stressed that physicians seeking to hydrate patients with chronic kidney disease and impaired left ventricular function should proceed cautiously. One of the recommended hydration regimens in the presence of chronic kidney disease is 1 mL/kg per hour for 12 hours before and

after PCI for patients with normal ejection fraction; for patients with moderately or severely reduced ejection fraction, a recommended hydration regimen consists of volume replacement matching urine output to maintain a euvolemic state for 12 hours before and after PCI.

SODIUM BICARBONATE

Two prospective, randomized trials showed that preventive hydration with sodium bicarbonate before and after contrast administration was more effective than hydration with sodium chloride for prophylaxis of CIN.^{14,15} In the single-center study by Merten et al, 119 patients with baseline serum creatinine levels of at least 1.1 mg/dL were randomized before exposure to iopamidol to receive a 154-mEq/L infusion of either sodium chloride (n=59) or sodium bicarbonate (n=60; a bolus of 3 mL/kg per hour for 1 hour followed by an infusion of 1 mL/kg per hour for the duration of the procedure and for 6 hours after the procedure).¹⁴ The primary endpoint of CIN (increase of $\geq 25\%$ in serum creatinine within 2 days of contrast exposure) occurred significantly less frequently in patients hydrated with sodium bicarbonate compared with patients hydrated with sodium chloride (1.7% vs 13.6%, respectively; $P=.02$).

The subsequent larger dual-center, randomized, double-blind study by Briguori et al compared three different strategies for preventing CIN in 326 patients with chronic kidney disease (baseline serum creatinine level ≥ 2 mg/dL and/or eGFR < 40 mL/min per 1.73 m^2) who underwent coronary or peripheral angiography and/or angioplasty.¹⁵ The patients were randomly assigned to prophylactic administration of 0.9% saline infusion plus N-acetyl-L-cysteine (NAC) (n=111), sodium bicarbonate infusion (using the protocol proposed by Merten et al¹⁴) plus NAC (n=108) and 0.9% saline plus ascorbic acid plus NAC (n=107). The rate of CIN (increase $\geq 25\%$ of serum creatinine concentration) was significantly lower ($P=.01$) in the bicarbonate plus NAC group (1.9%) than in the saline plus NAC group (9.9%), whereas the rate of CIN was practically identical between the saline plus NAC group and the saline plus ascorbic acid plus NAC group (9.9% vs 10.3%; $P=1$).

NAC

There has been ongoing debate as to whether NAC, an agent with antioxidant properties, is effective in the prevention of CIN. The rationale for the possible efficacy of NAC is based on the assumption that CIN is caused by reactive oxygen species, formed as a result of contrast media's direct toxic effect on tubular epithelial cells. In the first randomized placebo-controlled study of 83 patients exposed to contrast media, prophylactic oral administration of NAC along with hydration was superior to hydration alone in preventing CIN in patients with elevated baseline creatinine

levels.¹⁶ The rates of CIN in this study were 2% in NAC group compared with 21% in controls. The subsequent APART trial, including 54 patients and using a similar design, confirmed these results: CIN occurred in 8% of patients in the oral NAC group versus 45% in the placebo group.¹⁷

Further studies, however, did not confirm the efficacy of NAC in preventing CIN. In a randomized study of 183 patients, although the trial lacked placebo control, oral NAC plus hydration failed to show a significant difference in CIN rates compared to hydration alone.¹⁸ The benefit of NAC in this study was statistically significant only in patients who received a relatively small volume of contrast (≤ 140 mL).¹⁸ Similarly, in the largest randomized study investigating this issue to date (487 patients), intravenous NAC (500 mg) was ineffective in preventing CIN in patients with impaired renal function.¹⁹

The results of several meta-analytic studies on the use of NAC are inconsistent as well: two reports supported the use of NAC in reducing rates of CIN, whereas two others showed no evidence of NAC efficacy in preventing the condition.²⁰⁻²³ In a recent small randomized study of 20 consecutive male patients undergoing elective endovascular abdominal aortic aneurysm repair, standard intravenous fluid hydration plus NAC orally (600 mg twice a day for 2 days) did not result in lower rates of CIN compared with standard intravenous fluid hydration alone.²⁴

DOPAMINE

Due to its dilatory effect on the renal vasculature and the ability to increase renal blood flow and GFR, dopamine was thought to be useful in prevention of CIN. However, the results of clinical studies are conflicting. In one study, dopamine was shown to attenuate the increase in serum creatinine level after exposure to contrast media,²⁵ although in other studies, such an effect was either not documented²⁶ or was found only in patients with creatinine levels ≥ 2 mg/dL.²⁷ Moreover, in patients with peripheral vascular disease and CIN, the effect of dopamine on renal function was found to be deleterious.^{25,28}

FENOLDOPAM

Fenoldopam, a selective, dopamine-1 receptor agonist, known to produce both systemic and renal arteriolar vasodilatation, was shown to blunt the decline in renal blood flow and GFR in animals exposed to contrast media.²⁹ In a double-blind, randomized, placebo-controlled pilot trial, a combination of fenoldopam and hydration resulted in an increase in renal plasma flow, a decrease in peak serum creatinine level 72 hours after exposure to contrast media, and a trend for a decreased incidence of CIN compared with hydration alone (21% and 41%, respectively; $P=.14$).³⁰ Another small study reported no efficacy with fenoldopam

in preventing CIN. Allaqaband et al randomized 123 patients with baseline renal insufficiency to receive saline, fenoldopam (0.1 µg/kg per min), or NAC orally (600 mg) plus saline every 12 hours for 24 hours before and 24 hours after the procedure. CIN (serum creatinine increase ≥ 0.5 mg/dL within 48 hours) occurred in 15.3% of the saline group, 15.7% of the fenoldopam group, and 17.7% of the NAC group ($P=.92$).³¹

In the largest randomized radiocontrast study to date (the CONTRAST trial), 315 patients undergoing invasive cardiac procedures with a calculated creatine clearance <60 mL/min were hydrated and then randomized to either placebo or fenoldopam (0.05 µg/kg per min, titrated up to 0.10 µg/kg per min) starting 1 hour before catheterization and continuing for 12 hours after.³² The incidence of CIN, defined as an increase in serum creatinine of $\geq 25\%$ from baseline to the maximum value obtained within the 24- to 96-hour period after completion of study drug administration, occurred in 33.6% of the fenoldopam group versus 30.1% of control patients ($P=.54$). No subgroup was identified that demonstrated even a trend toward benefit with fenoldopam. Thus, fenoldopam cannot be recommended for prophylactic use in patients at high risk for CIN.

THEOPHYLLINE

Several studies have provided evidence of adenosine involvement in the renal hemodynamic response to contrast media.^{33,34} This raised the hypothesis that theophylline, an adenosine A1-receptor antagonist, may attenuate the decrease in renal blood flow and GFR induced by exposure to contrast media. In a randomized, placebo-controlled study, prophylactic intravenous administration of 200 mg theophylline reduced the incidence of CIN in patients with chronic kidney disease (4% in patients treated with theophylline vs 16% in patients treated with placebo).³⁵ In another randomized, placebo-controlled study,³⁶ treatment with theophylline was accompanied by a smaller decrease in GFR, plasma erythropoietin, and rennin, and a smaller increase in urinary beta-2-microglobulin compared with placebo. However, three other randomized studies did not show any benefit with theophylline compared to placebo in preventing CIN.^{28,37,38} Finally, two meta-analyses of published studies showed that prophylactic administration of theophylline or aminophylline protects against radiocontrast-induced decline in kidney function.^{39,40}

OTHER TREATMENT MODALITIES

As a result of observations of contrast-induced alterations in calcium metabolism and the ability of calcium channel antagonists to relieve vasoconstriction, several studies investigated the effect of calcium channel blockers on CIN prevention. In a small randomized study (35 patients),

nitrendipine showed an ability to preserve GFR, whereas patients treated with placebo experienced a decrease in GFR.⁴¹ However, in two other studies, the change in creatinine level did not differ significantly between groups.^{42,43} Atrial natriuretic peptide, meanwhile, failed to prevent CIN in a randomized, placebo-controlled study of three different doses.⁴⁴

Based on the decreased levels of prostaglandins in patients with CIN, it was hypothesized that prophylactic administration of prostaglandin E1 may be beneficial in reducing CIN.⁴⁵ A double-blind, randomized, placebo-controlled study investigated the effect of intravenous administration of prostaglandin E1 in three different doses, showing that patients treated with prostaglandin E1 experienced a significantly smaller increase in serum creatinine levels independent of the given dose after exposure to contrast media compared with placebo.

Two retrospective series analyzed the efficacy of pretreatment with statins on the development of CIN in patients undergoing cardiac catheterization.^{46,47} The first study focused on 1,002 patients with a baseline serum creatinine level ≥ 1.5 mg/dL undergoing cardiac catheterization who did not receive statins before admission. Compared with patients who were not pretreated with statins ($n=752$), the mean serum creatinine level after the procedure and the subsequent rates of CIN were significantly lower among patients who did receive pretreatment with statins ($n=250$) before exposure to nonionic, low-osmolality contrast.⁴⁶ In the larger series from the same institution focusing on baseline preprocedure and peak postprocedure serum creatinine values in 29,409 patients, preprocedural treatment with statins demonstrated a lower incidence of CIN (4.4% vs 5.9%; $P<.0001$) and requirement for dialysis (0.32% vs 0.49%; $P=.03$).⁴⁷ After adjustments for comorbidities, preprocedural statin use was an independent predictor of freedom from CIN.⁴⁷

Several studies examined the effect of hemodialysis immediately after exposure to contrast media in preventing renal function deterioration in patients with pre-existing chronic kidney disease. In two studies, prophylactic hemodialysis failed to diminish the rates of CIN^{48,49} and even increased them in one study.⁴⁸ However, in a recent prospective, randomized study by Lee et al, prophylactic hemodialysis improved renal outcomes in 82 patients with chronic kidney disease undergoing coronary angiography (stable serum creatinine concentration of >3.5 mg/dL, with a change of <0.5 mg/dL within the last month).⁵¹ In this study, patients were randomized to receive either hydration with normal saline intravenously and prophylactic hemodialysis after the procedure ($n=42$) or hydration alone ($n=40$). Prophylactic hemodialysis was associated with a smaller decrease in creatinine clearance within 72 hours of

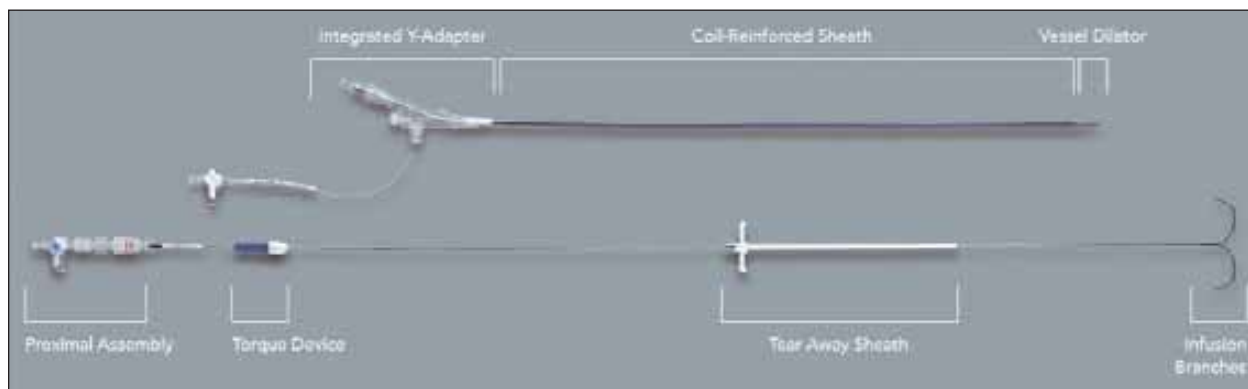


Figure 2. The Benephit Infusion System (FlowMedica, Inc., Fremont, CA).

contrast exposure (primary endpoint, 0.4 ± 0.9 mL/min per 1.73 m^2 vs 2.2 ± 2.8 mL/min per 1.73 m^2 ; $P < .001$), a lower level of serum creatinine at day 4 (5.1 ± 1.3 mg/dL vs 6.3 ± 2.3 mg/dL; $P = .01$), and lower rates of temporary renal replacement therapy (2% vs 35%; $P < .001$). Remarkably, 13% of control patients but none of the dialysis patients required long-term dialysis after discharge ($P = .018$).

One randomized study investigated the role of hemofiltration compared with isotonic-saline hydration (started 4 to 8 hours before exposure to contrast media and continued for 18 to 24 hours after exposure) in preventing CIN in patients with chronic kidney disease (serum creatinine concentration > 2 mg/dL) undergoing coronary interventions.⁵² Among 114 consecutive patients, CIN developed significantly less frequently in patients treated with hemofiltration (fluid replacement rate, 1,000 mL/h without weight loss) compared with patients treated with isotonic-saline hydration (1 mL/kg per hour; 5% vs 50%; $P < .001$). In addition, hemofiltration was associated with significantly lower rates of temporary renal-replacement therapy (3% vs 25%, respectively), in-hospital events (9% vs 52%), in-hospital mortality (2% vs 14%), and cumulative 1-year mortality rates (10% vs 30%).

Targeted renal therapy is a novel catheter-based approach aimed at delivery of renal vasodilator agents such as fenoldopam, a selective dopamine-1 receptor agonist, and nesiritide, a B-type natriuretic peptide, directly to the kidneys via the renal arteries using the Benephit Infusion System to maximize the beneficial kidney effects of drugs while minimizing systemic side effects (Figure 2). In a randomized, controlled, open-label, partial crossover design trial, 33 patients who underwent coronary angiography were randomized in a 1:2 ratio to control or fenoldopam (initially administered intravenously, then crossed over to bilateral selective infusion to renal arteries).⁵³ Selective administration of fenoldopam was associated with a significantly higher GFR and renal plasma flow, lower fenoldopam plasma levels, and greater nadir systolic blood pressure.⁵³ In

the Benephit System Renal Infusion Therapy (Be-RITE) Multicenter Registry, among a total of 366 patients (61% diabetics, mean baseline creatinine clearance 37.1 mL/min, and serum creatinine 2.1 mg/dL) enrolled at 16 sites worldwide, local administration of medications (fenoldopam, sodium bicarbonate, alprostadil, and nesiritide) was safe and required a mean of 2 minutes to obtain bilateral renal artery access with 9.4% rates of CIN, lower than 30.6% expected rates.⁵⁴ Another ongoing trial is addressing the issue of whether local drug delivery will allow the reduction of CIN rates in patients undergoing contrast medium exposure.⁵⁵

CONCLUSION

The best approach to prevent CIN is to identify at-risk patients, provide adequate periprocedural hydration, and minimize the amount of contrast administered. Hydration with sodium bicarbonate has been shown to be beneficial compared with hydration with sodium chloride and should be recommended in patients with chronic kidney disease. So far, no single agent has shown a consistent benefit above and beyond hydration in preventing CIN. Study results are mixed as to whether prophylactic oral NAC reduces the incidence of CIN, although its use is generally recommended given its low cost and favorable side-effect profile. Agents that have been shown to be ineffective or harmful, or for which data supporting routine use do not exist, include fenoldopam, theophylline, dopamine, calcium-channel blockers, prostaglandin E1, and atrial natriuretic peptide. The efficacy of statins to prevent CIN should be evaluated in a prospective randomized trial. Prophylactic hemodialysis and hemofiltration may represent an important option to prevent CIN in the highest-risk cohort, although further studies of these invasive modalities are needed. Given the complex logistics coupled with the high cost of hemofiltration, hemodialysis might represent a more feasible approach to the prevention of CIN in high-risk patients with advanced chronic kidney disease. Several novel pharmacologic agents and devices that offer promise in reducing the development

of CIN are currently undergoing investigation, with the goal of improving the long-term prognosis for patients who must receive contrast media during invasive diagnostic and interventional therapeutic procedures. ■

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