Recent Clinical Trials of Iodixanol

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In patients with well-preserved renal function, the choice of contrast agent appears to have little impact on the development of contrast-induced nephropathy (CIN). However, in patients with underlying renal insufficiency and diabetes mellitus, it has been shown that the use of low-osmolar media is associated with a lower incidence of CIN compared with high-osmolar agents. Previously, it was unknown whether further benefit would be derived from the use of iso-osmolar contrast media. Recent studies, including Nephrotoxicity in High-Risk Patients Study of Iso-osmolar and Low-Osmolar Nonionic Contrast Media (NEPHRIC), have shown a reduction in the incidence of CIN with the iso-osmolar contrast agent iodixanol compared with low-osmolar agents in patients with renal insufficiency and diabetes. The peak rise in serum creatinine was significantly reduced with iodixanol (0.13 mg/dL vs 0.55 mg/dL, P < .001). The incidence of CIN, defined as a peak rise > 0.5 mg/dL, was decreased from 26% to 3%, P < .0002 when iodixanol was used. An ongoing, multicenter, prospective, double-blind, randomized study (Visipaque Angiography/Interventions with Laboratory Outcomes for Renal Insufficiency [VALOR]) is evaluating the potential benefit of iodixanol in reducing CIN in patients with preexisting renal impairment. Accumulating evidence suggests that the use of iso-osmolar contrast agents in conjunction with other proven measures, especially adequate intravenous hydration and contrast dosage limitation, can reduce the morbidity and mortality associated with CIN. These measures have the potential for a significant reduction in health care costs.

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Early contrast agents were ionic monomers and were hypertonic compared with human serum (approximately 1500–1800 mOsm/kg). A relatively high frequency of cardiac and renal adverse effects was noted following their use. This led to the development of newer agents that had lower osmolality and were less chemotoxic. These second-generation nonionic contrast agents

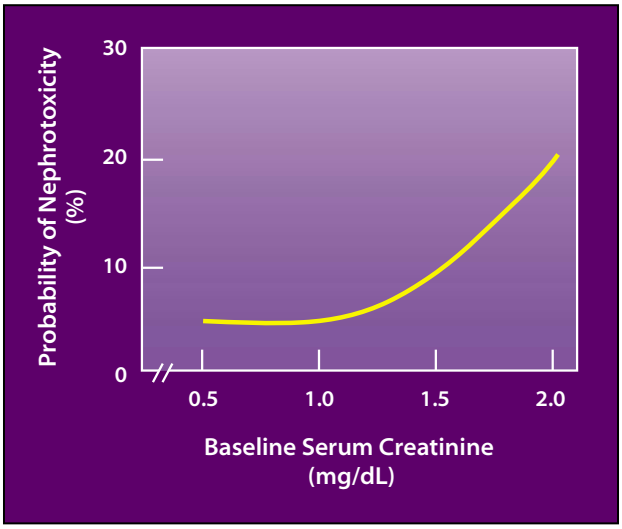

Figure 1. *Risk of contrast-induced nephropathy based on serum creatinine at baseline. Adapted from Davidson et al.*[2]

were monomers of iodinated benzene rings (eg, iohexol, iopamidol). Although the osmolality of these agents was lower than that of conventional ionic agents, they were still hyperosmolar relative to plasma (approximately 600–850 mOsm/kg). The most recently developed class of contrast media is a nonionic dimer. Iodixanol is the first, and is novel in that it is iso-osmolar to plasma at all iodine concentrations (approximately 290 mOsm/kg).

The renal toxicity of iodinated contrast agents has been well described (Figure 1).[1–3] Although the exact mechanism is unclear, studies in experimental animals have postulated that renal vasoconstriction, direct toxic effects, and ischemia are possible explanations. Risk factors for the development of contrast-induced nephropathy (CIN) include preexisting renal insufficiency, diabetes mellitus, dehydration, advanced age, use of diuretics, and uncontrolled hypertension. Patients who have both diabetes and preexisting renal insufficiency have been shown to be at the highest risk for developing CIN.[4] There is no universally accepted quantitative definition of CIN; the most commonly used criteria include an absolute increase in the serum creatinine (SCr) concentration of at least 0.5 mg/dL (44.2 mmol/L) or a relative increase of at least 25% from the baseline value.

Previous studies demonstrated that in patients with preserved renal function, the choice of contrast agent had no impact on the development of CIN.[3] Analysis of patients with diabetes and/or baseline renal insufficiency has shown that contrast media osmolality is an important factor in CIN. In a prospective, randomized trial involving 1196 patients, it was shown that among patients without diabetes but with renal insufficiency (baseline SCr concentrations >1.5 mg/dL), the incidence of nephropathy (defined as an increase of 0.5 mg/dL in the SCr concentration within 72 hours after contrast administration) was reduced from 27% to 12% by the use of the nonionic low-osmolar agent iohexol in comparison with the ionic high-osmolar agent diatrizoate.[4] Among patients with both diabetes and renal insufficiency, the incidence was reduced from 48% to 33%. Overall, patients receiving high-osmolar contrast agents were more than three times as likely to have CIN as those receiving low-osmolar agents ($P < .0013$). Additionally, in a meta-analysis of trials with high- and low-osmolality contrast media, Barrett and Carlisle[1] found that the use of low-osmolar contrast agents conferred a statistically significant benefit for patients with baseline renal insufficiency when compared with high-osmolar agents (odds ratio, 0.44; CI, 0.26-0.73).

Although these trials showed that the use of nonionic, low-osmolar contrast media was associated with lower rates of CIN, it was unknown whether further benefit would be derived from iso-osmolar contrast media. Some animal models suggested that renal blood flow was decreased with iodixanol when compared with low-osmolar contrast media because of increased plasma viscosity (associated with increased molecule size and weight). There was concern that this increased viscosity would lead to sludging of red blood cells in the microcirculation of the medulla, subsequently leading to ischemia.[5]

Several recent studies, including Chalmers and Jackson,[6] the Nephrotoxicity in High-Risk Patients Study of Iso-osmolar and Low-Osmolar Nonionic Contrast Media (NEPHRIC) trial,[7] the Rapid Protocol for the Prevention of Contrast-Induced Renal Dysfunction (RAPPID) trial,[8] and the ongoing Visipaque Angiography/Interventions with Laboratory Outcomes for Renal Insufficiency (VALOR) trial, address the use of iso-osmolar contrast media (iodixanol) and its effects on CIN in high-risk patient populations (baseline renal insufficiency and/or diabetes).

Pharmacology

The osmolality of contrast agents is a function of the size of the molecules that compose the agent and the number of particles in solution. Iso-osmolar nonionic contrast agents reduce osmolality by linking two

molecules of iodinated benzene rings together, creating a dimer. This is done through the use of a common side chain and results in a large molecule in solution. Because there is only one particle in solution for every six iodine atoms, the ratio becomes 6:1. Iodixanol is the first contrast agent available in the United States in this class.

Clinical Trials

Chalmers and Jackson[6] compared the use of an iso-osmolar, dimeric, nonionic contrast agent (iodixanol) to a low-osmolar, nonionic, monomeric contrast agent (iohexol) in a population of patients with preexisting renal impairment. In this trial, 124 patients who had SCr >1.7 mg/dL (150 µmol/L) presenting for renal and/or peripheral angiography were randomized to receive either iohexol or iodixanol. SCr was measured within 48 hours prior to angiography, then at 24 hours and at variable intervals postprocedure. Follow-up was available for 102 of the 124 study participants, 54 of whom had been randomized to the iodixanol group and 48 to the iohexol group.

The study found that 15 of 48 patients (31%) in the iohexol group had a rise >10% in SCr, compared with eight of 54 patients (15%) in the iodixanol group ($P < .05$). SCr values rose by more than 25% in five of 48 patients (10%) in the iohexol group, compared with two of 54 (3.7%) in the iodixanol group. The creatinine rise was positively correlated with the dose of both contrast media.

This study was the first to suggest that iodixanol could exert a beneficial effect on the prevention of CIN. One third of patients in this study had diabetes mellitus. However, the sample size was small, contrast selection was unblinded, and a low contrast dosage (50–60 mL) was used. In addition, the authors stated that a subset underwent additional interventions as well as changes in drug therapy during the week following angiography. These factors may have contributed to the change observed in SCr. Nevertheless, the positive correlation between dosage of contrast media and differences in the change in creatinine suggests a potential causal role. This preliminary study demonstrated a statistically significant but clinically modest difference in the incidence of nephrotoxicity with iodixanol compared with iohexol in patients with chronic renal impairment.

The NEPHRIC study demonstrated that mean peak SCr concentration increased significantly less in patients who received iodixanol compared with iohexol.

The NEPHRIC study by Aspelin and colleagues[7] was a prospective, double-blinded, randomized, placebo-controlled trial that compared the iso-osmolar agent iodixanol to the nonionic low-osmolar agent iohexol in patients at high risk for developing CIN. The study involved 129 patients who were defined as high risk by the presence of diabetes with SCr concentrations of 1.5 mg/dL to 3.5 mg/dL for men and 1.3 mg/dL to 3.5 mg/dL for women. Patients presenting for coronary or aortofemoral angiography were included and were randomized to receive either iodixanol or iohexol. The primary endpoint was the peak increase in SCr within the 3 days following angiography. Secondary endpoints included an increase in creatinine concentration of 0.5 mg/dL or more, an increase of 1.0 mg/dL or more, and the change in creatinine concentration over the 7 days following angiography.

The study demonstrated that mean peak SCr concentration increased significantly less in patients who received iodixanol compared with iohexol. The peak increase in creatinine over 3 days was 0.13 mg/dL for iodixanol versus 0.55 mg/dL for iohexol ($P = .001$) (Table 1). Using an increase in creatinine of 0.5 mg/dL as the definition of CIN, 3% of the iodixanol group versus 26% of the iohexol group suffered CIN ($P = .002$). The odds ratio for iodixanol-associated CIN > 0.5 mg/dL was 0.09 (0.02-0.41). If an increase in creatinine of 1.0 mg/dL was used, the incidence of CIN was 0% in the iodixanol group and 15% in the iohexol group (Figure 2).

The baseline demographic charac-

Table 1
Peak Increase in Serum Creatinine Concentration from Baseline to Day 3 from the NEPHRIC Trial

Group	Patients (n)	Increase in Serum Creatinine Concentration (mg/dL)*		
		Mean ± SD (95% CI)	Median	Range
Iodixanol	64	0.13 ± 0.22 (0.08–0.18)	0.10	-0.21–0.84
Iohexol	65	0.55 ± 0.98 (0.36–0.85)	0.21	-0.24–5.42

*To convert values for creatinine to µmol/L, multiply by 88.4.
Adapted with permission from Aspelin et al.[7]

teristics of the two groups were similar with respect to age, weight, body mass index, baseline SCr, hydration status, and volume of contrast used. The average duration of diabetes, however, was noted to be significantly longer in the iohexol group than in the iodixanol group (18.0 years vs 12.8 years). However, the duration of diabetes in patients as a specific risk factor for the development of CIN has not been demonstrated.

The volume of hydration received by the two groups (mean volume 977 mL in the iodixanol group and 934 mL in the iohexol group) reflects the usual standard of care for this population. Although differences in hydration status are known to contribute to the development of CIN, the optimal volume and rate of hydration required to minimize the risk of CIN are unknown. Because of differences in baseline hydration status and left ventricular function, hydration must be tailored to the individual patient. A balance between adequate hydration and avoidance of precipitation of congestive heart failure is the goal. In this study, similar amounts of hydration were used in the two groups, further supporting the results obtained.

Although the use of angiotensin-converting-enzyme (ACE) inhibitors is not specifically mentioned in the article, the authors stated in a later correspondence that 78% of patients in the iodixanol group were using ACE inhibitors, versus 55% in the iohexol group.[9] The relative contribution of this difference to the risk of developing CIN is unclear.

The NEPHRIC trial was primarily a trial of diagnostic angiography rather than percutaneous coronary intervention (PCI) (17% rate of PCI in the iodixanol group versus 25% in the iohexol group). Although the mean contrast dosages used in this trial (163 mL in the iodixanol group and 162 mL in the iohexol group) were larger than those used by Chalmers and Jackson (60 mL in the iodixanol group and 52 mL in the iohexol group), they were potentially lower than the levels required for complex PCI or combined diagnostic and therapeutic procedures. Future studies will be required to evaluate the protective effect of iodixanol when larger doses of contrast media are used.

Ultimately, the clinical impact of the NEPHRIC trial is that it not only confirms the results of the smaller Chalmers study, but also extends the results to a population at higher risk for CIN (ie, patients with diabetes and baseline renal insufficiency).

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The RAPPID[8] study was designed to investigate the potential benefit of using N-acetylcysteine (NAC) in conjunction with iodixanol. In this prospective randomized study, 80 patients with stable renal dysfunction (SCr concentration > 1.36 mg/dL or creatinine clearance < 50 mL/min) received a protocol of intravenous (IV) NAC versus IV hydration alone while undergoing cardiac catheterization or intervention. Forty-one patients in the NAC group received 150 mg/kg NAC in 500 mL of normal saline over 30 minutes immediately before contrast, followed by 50 mg/kg in 500 mL of normal saline over 4 hours. Thirty-nine patients in the IV hydration group received 1 mL/kg/hr of normal saline for 12 hours pre- and postcontrast. All patients received iodixanol during their coronary studies. CIN was defined as an increase in SCr concentration by 25% at either 2 or 4 days after contrast administration.

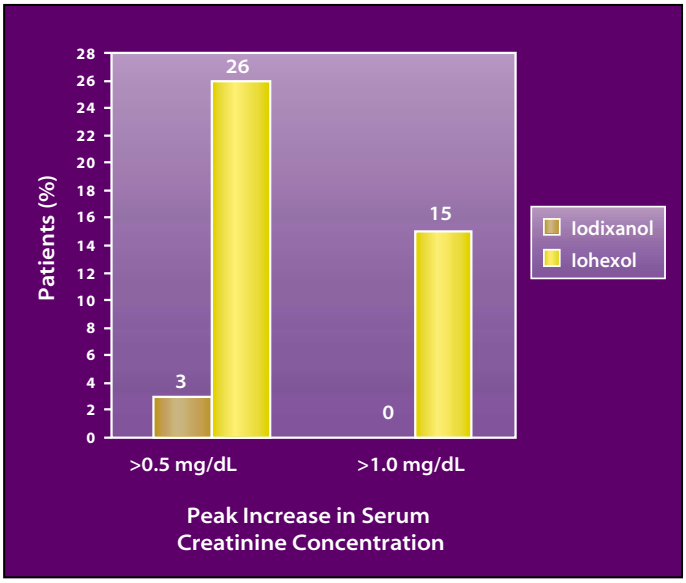

Figure 2. *Differences in contrast-induced nephropathy between iodixanol and iohexol from the NEPHRIC trial. The bars show the percent of patients with a maximal increase in serum creatinine concentration between day 0 and day 3 of at least 0.5 mg/dL and at least 1.0 mg/dL (P = .002). Adapted with permission from Aspelin et al.*[7]

At 48 and 96 hours after the procedure, 76 out of 80 and 74 out of 80 patients had SCr measurements available for analysis.

The study found that CIN occurred in 2 of the 41 patients in the NAC group (5%) and in 8 of the 39 patients in the hydration group (21%; $P = .045$). In the NAC group, mean SCr fell from 1.85 mg/dL to 1.77 mg/dL at 48 hours and 1.79 mg/dL at 96 hours postcontrast, respectively ($P = .02$ and .023 vs baseline). In the hydration group, SCr increased from 1.75 mg/dL to 1.81 mg/dL at 48 hours and 1.80 mg/dL at 96 hours postcontrast, respectively ($P = .99$ and .23 vs baseline).

The potential benefit of using oral NAC in conjunction with iodixanol in a high-risk patient population deserves further study.

The major finding of this study was that treatment of patients with IV NAC and normal saline started immediately before the coronary procedure reduced the incidence of CIN compared with a standard protocol of saline hydration alone. This study also found that the absolute change in SCr concentration was less in NAC-treated patients than in the hydration-alone group. However, the sample size was small, the rate of fluid administration differed, and the definition of CIN was liberal.

The reduction in the incidence of CIN shown in the RAPPID trial was similar to previous trials in which patients received oral NAC.[10] This provides preliminary support for the combined benefit and safety of IV NAC used in conjunction with iodixanol. The potential benefit of using oral NAC in conjunction with iodixanol in a high-risk patient population deserves further study.

The VALOR study is an ongoing, multicenter, prospective, randomized, double-blind trial comparing the renal effects of the iso-osmolar contrast agent iodixanol to the low-osmolar contrast agent ioversol in subjects with elevated SCr undergoing coronary angiography or interventions. The use of NAC is at the discretion of the operator. Subjects with stable renal insufficiency, defined as elevated SCr (≥ 1.7 mg/dL for men, ≥ 1.5 mg/dL for women), are randomized to receive an iso-osmolar contrast agent (iodixanol) or a low-osmolar contrast agent (ioversol). SCr values are measured at 24, 48, and 72 hours following contrast administration. The primary end points are mean peak change in creatinine (peak postcontrast administration minus baseline) up to 72 hours postprocedure and the proportion of patients with an increase in SCr of at least 0.5 mg/dL. Secondary endpoints include a comparison of iodixanol and ioversol with regard to their rates of CIN using a more stringent definition (an increase ≥ 1.0 mg/dL) and mean percent changes in calculated glomerular filtration rate.

The novel aspect of this study is the large multicenter, high-risk population receiving double-blind administration of contrast media. The study should closely reflect current medical practice, including subjects with impaired renal function, diabetics, and discretionary use of NAC. In addition, a health economic analysis is planned to elucidate the potential cost:benefit of this agent.

Commentary

The recent and ongoing clinical trials with iodixanol are important to formulate an appropriate strategy to reduce the risk of CIN during angiographic procedures. There is growing evidence that the use of an iso-osmolar contrast agent reduces the risk of CIN in a high-risk patient population when compared with a low-osmolar contrast agent.

The prognostic importance of lowering the incidence of CIN has been studied.[11] CIN is a major determinant of mortality and morbidity following coronary angiography and interventional procedures. In 7586 patients who had undergone PCI, it was demonstrated that in 254 (3.3%) who experienced CIN, there was increased mortality during the index hospitalization as well as at 5 years. Patients who developed CIN did have higher rates of other comorbidities, including congestive heart failure, diabetes, myocardial infarction within 24 hours of PCI, and peripheral vascular disease. Subsequent studies controlling for comorbidities, including a retrospective matched-pairs cohort study by Levy and coworkers,[12] have also shown higher mortality for patients with CIN. Although there are no prospective randomized trials proving that lowering the incidence of CIN will result in improved outcomes,

There is growing evidence that the use of an iso-osmolar contrast agent reduces the risk of CIN in a high-risk patient population when compared with a low-osmolar contrast agent.

Table 2
Periprocedural Considerations:
Prevention of Contrast-Induced Nephropathy

1) Discontinue nonsteroidal anti-inflammatory drugs.
2) Discontinue metformin for at least 48 hours after procedure.
3) Administer 1–2 liters of 0.9 normal saline over 12–24 hours before and after procedure at a rate of 1.5 mL/kg/hr or 150 mL/hr for a target urinary output of 150 mL/hr in the 6 hours after the procedure. AVOID DEHYDRATION.
4) Limit dosage of contrast medium to <30 mL for diagnostic studies and 100 mL for combined diagnostic and percutaneous coronary intervention (PCI) cases. Use biplane angiography when available.
5) If PCI is complex, stage PCI at least 10 days after diagnostic procedure or as long as feasible if the patient is in the hospital.
6) Administer iso-osmolar contrast medium (eg, iodixanol).
7) Avoid contrast medium readministration during recovery phase of acute tubular necrosis.

these data suggest the existence of an adverse outcome relationship with CIN. The effects are particularly pronounced in patients with underlying renal insufficiency and diabetes.

The metabolic explanation for iso-osmolar contrast media possessing less nephrotoxicity than low-osmolar contrast media is not well understood. Hypotheses have included the extent of osmotic diuresis being less with iso-osmolar media (leading to decreased renal tubular enzyme secretion following contrast exposure) and differences in the extent of chemotoxicity between agents. Regardless of the specific mechanism, a clinical benefit does exist with the use of iso-osmolar agents and appears to be greater in patients with baseline renal insufficiency with or without diabetes.

The cardioprotective effect of iso-osmolar contrast media compared with low-osmolar agents was addressed in the recent COURT (Contrast Utilization in High-Risk Patients Undergoing PTCA [percutaneous transluminal coronary angioplasty]) trial.[13] In this multicenter, prospective, randomized, double-blind trial of 856 high-risk patients, the cohort receiving iodixanol experienced a 45% reduction in major adverse clinical events when compared with the cohort receiving a low-osmolar contrast agent (ioxaglate) ($P < .001$). The benefit was particularly striking in patients who had not received an IV IIb/IIIa platelet inhibitor with their intervention (1.7% vs 8.1%; $P < .0001$). Thus, iso-osmolar contrast prevented major cardiac adverse events following PCI performed during acute coronary syndromes.

Guidelines for Prevention of CIN

Although additional data will be necessary, the available evidence allows several general renoprotective strategies to be proposed (Table 2). Adequate pre- and postprocedure IV hydration, limitation of contrast dosage, and lengthening of the time interval between procedures have been shown to confer benefit. Of these, IV hydration is the most important. Solomon and associates[14] showed that hydration with 0.45% saline for 12 hours before and 12 hours after the administration of contrast agents was the most effective means of preventing acute decreases in renal function in patients with or without diabetes mellitus. Subsequent studies have shown further benefit with the use of normal saline as opposed to 0.45% saline, and this should be considered the choice for IV hydration regimens.[15]

Additional recommendations include limiting the dosage of contrast used during procedures in patients with underlying renal insufficiency to < 30 mL for diagnostic angiography and < 100 mL for PCI. When feasible, it is preferable to stage PCI 48 hours following the administration of iso-osmolar contrast agents in patients with renal insufficiency. Furthermore, the avoidance of contrast during the recovery phase of acute tubular necrosis and discontinuance of nonsteroidal anti-inflammatory drugs, ACE inhibitors, and metformin for 48 hours following procedures are effective renoprotective strategies.

Several strategies have not been successful in reducing the incidence of CIN. Solomon and colleagues[14] found that neither forced diuresis with mannitol nor furosemide offered additional protection against CIN compared with saline hydration alone in either diabetic or nondiabetic patients. Low-dose dopamine infusion has been observed to increase renal blood flow but was associated with a higher incidence of CIN in diabetic patients.[16] The recently published CONTRAST trial evaluated a selective IV dopamine agonist, fenoldopam. It demonstrated no benefit in the prevention of CIN.[17] Endothelin-receptor antagonists have not been shown to reduce the risk of

CIN in patients with underlying renal dysfunction. In fact, patients treated with this agent and IV hydration had a significantly higher incidence of CIN compared with patients treated with IV hydration alone (56% vs 29%, $P = .002$).[18] In examining the effects of calcium-channel blockers on patients with renal insufficiency; it was shown that daily treatment with nifedipine did not appear to exert a protective effect after administration of a contrast agent.[19]

Cost-Effectiveness

CIN is associated with higher health care costs, primarily through lengthening hospital stays and the initiation of dialysis in certain patients. Reduction in the incidence of CIN will likely have public health benefits both through a reduction in mortality associated with CIN and a relative decrease in health care costs by reducing hospital stay or the need for dialysis. Thus, although the use of iso-osmolar agents is more expensive than low-osmolar agents (approximately $35 per 100 mL vs $20–$25 per 100 mL), this additional cost could be offset by savings in other hospital-related expenditures. When compared with other therapies already used in the cardiac catheterization laboratory to reduce morbidity and mortality (eg, drug-eluting stents, which are approximately $2000 more than bare metal stents), the relative increase in cost is modest.

A study by Powe and colleagues[20] showed that the higher material cost of low-osmolality agents in angiography was partially offset by a reduction in the cost management of adverse drug reactions associated with low-osmolality versus high-osmolality media. A similar economic analysis would be beneficial in assessing the cost-effectiveness of iso-osmolar agents and will be addressed in the ongoing VALOR trial.

Summary

Iso-osmolar agents have documented renoprotective benefits for use in a high-risk population. They appear to be safe and well tolerated, and are likely to be proven cost-effective. Thus, for patients with underlying renal insufficiency, iso-osmolar agents provide a valuable addition to preventive strategies currently available for the reduction of CIN. ■

References

1. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. *Radiology*. 1993;188:171–178.
2. Davidson CJ, Hlatky M, Morris KG, et al. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. *Ann Intern Med*. 1989;110:119–124.
3 Schwab SJ, Hlatky M, Pieper KS, et al. Contrast nephrotoxicity: a randomized controlled trial of a nonionic and an ionic radiographic contrast agent. *N Engl J Med*. 1989;320:149–153.
4. Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. The Iohexol Cooperative Study. *Kidney Int*. 1995;47:254–261.
5. Deray G, Bagnis C, Jacquiaud C, et al. Renal effects of low and iso-osmolar contrast media on renal hemodynamics in a normal and ischemic dog kidney. *Invest Radiol*. 1999;34:1–4.

Main Points

- Analysis of patients with diabetes and/or baseline renal insufficiency has shown that contrast media osmolality is an important factor in contrast-induced nephropathy (CIN). In a prospective, randomized trial involving 1196 patients, it was shown that among patients without diabetes but with renal insufficiency, the incidence of nephropathy was reduced from 27% to 12% by the use of the nonionic low-osmolar agent iohexol in comparison with the ionic high-osmolar agent diatrizoate.
- The NEPHRIC study demonstrated that mean peak SCr concentration increased significantly less in patients who received iodixanol compared with iohexol.
- The RAPPID study showed that intravenous (IV) N-acetylcysteine (NAC), initiated before exposure to iodixanol, reduced the rate of CIN compared to the control group. A large, randomized trial of NAC is needed to confirm this trial.
- The novel aspect of the VALOR study is the large multicenter, high-risk population receiving double-blind administration of contrast media. The study should closely reflect current medical practice, including subjects with impaired renal function, diabetics, and discretionary use of NAC.
- In the COURT trial, the cohort receiving iodixanol experienced a 45% reduction in major adverse clinical events when compared with the cohort receiving a low-osmolar contrast agent (ioxaglate).
- Adequate pre- and postprocedure IV hydration, limitation of contrast dosage, and lengthening of the time interval between procedures have been shown to confer benefit. Of these, IV hydration is the most important.
- Reduction in the incidence of CIN will likely have public health benefits both through a reduction in mortality associated with CIN and a relative decrease in health care costs by reducing hospital stay or the need for dialysis.

6. Chalmers N, Jackson RW. Comparison of iodixanol and iohexol in renal impairment. *Br J Radiol*. 1999;72:701–703.
7. Aspelin P, Aubry P, Fransson S, et al. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med*. 2003;348:491–499.
8. Baker CS, Wragg A, Kumar S, et al. A rapid protocol for the prevention of contrast induced renal dysfunction: the RAPPID study. *J Am Coll Cardiol*. 2003;41:2114–2118.
9. Aspelin P, Berg KJ. Nephropathy induced by contrast medium [Letter to the Editor]. *N Engl J Med*. 2003;348:2257–2259.
10. Tepel M, van der Giet M, Schwarzfeld C, et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med*. 2000; 343:180–184.
11. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;105:2259–2264.
12. Levy EM, Viscoli CM, Horwitz RJ. The effect of acute renal failure on mortality: a cohort analysis. *JAMA*. 1996;275:1489–1494.
13. Davidson CJ, Laskey WK, Hermiller JB, et al. Randomized trial of contrast media utilization in high-risk PTCA: the COURT trial. *Circulation*. 2000;101:2172–2177.
14. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med*. 1994;331:1416–1420.
15. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media-associated nephropathy. *Arch Intern Med*. 2002; 162:329–336.
16. Weisberg LS, Kurnik PB, Kurnik BRC. Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. *Kidney Int*. 1994;45:259–265.
17. Stone GW, McCullough P, Tumlin J, et al. A prospective randomized placebo controlled multicenter trial evaluation fenoldopam mesylate for the prevention of contrast induced nephropathy: the CONTRAST Trial [abstract]. *J Am Coll Cardiol*. 2003;41:83A.
18. Wang A, Holcslaw T, Bashore T, et al. Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism. *Kidney Int*. 2000;57:1675–1680.
19. Cacoub P, Deray G, Baumelou A, Jacobs C. No evidence for protective effects of nifedipine against radiocontrast-induced acute renal failure [letter]. *Clin Nephrol*. 1988;29:215–216.
20. Powe NR, Davidoff AJ, Moore RD, et al. Net costs from three perspectives of using low versus high osmolality contrast medium in diagnostic angiocardiography. *J Am Coll Cardiol*. 1993;21:1701–1709.