

Contrast-Induced Nephropathy in Patients With Chronic Kidney Disease Undergoing Computed Tomography

A Double-Blind Comparison of Iodixanol and Iopamidol

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Background: Based on a single clinical trial, it has been suggested that the contrast agent iodixanol, which is isotonic to human plasma, may be less nephrotoxic than other nonionic contrast agents in renally impaired patients after intra-arterial injection. We compared the effects on renal function of iopamidol-370 injection (796 mOsm/kg) and iodixanol-320 (290 mOsm/kg) in patients with chronic kidney disease undergoing contrast-enhanced multidetector computed tomography (CE-MDCT) examinations using a multicenter, double-blind, randomized, parallel-group design.

Methods: A total of 166 patients with stable moderate-to-severe chronic kidney disease (screening and baseline serum creatinine, SCr, ≥ 1.5 mg/dL and/or creatinine clearance, CrCl, ≤ 60 mL/min) who were undergoing CE-MDCT of the liver or peripheral arteries were randomized to receive equi-iodine IV doses (40 gI) of either iopamidol-370 (370 mgI/mL) or iodixanol-320 (320 mgI/mL) at 4 mL/s. SCr and CrCl were obtained at screening, baseline, and at $48-72 \pm 6$ hours after dose (mean, 57.4 hours). Contrast-induced nephropathy (CIN) was defined as an absolute increase ≥ 0.5 mg/dL (44.2 $\mu\text{mol/L}$) and/or a relative increase in SCr $\geq 25\%$ from baseline.

Results: A total of 153 patients were included in the final analysis (13 patients excluded because of lack of follow-up, hemodialysis to

remove contrast, average daily CrCl variation $>1\%$ at screening). The 2 study groups were comparable with regard to age, gender distribution, the presence of diabetes, concomitant medications, hydration, and contrast dose. Mean pre-dose SCr was 1.6 ± 0.4 mg/dL in both groups ($P = 0.9$). An absolute increase ≥ 0.5 mg/dL (44.2 $\mu\text{mol/L}$) in SCr was observed in none of the patients receiving iopamidol-370 and in 2.6% (2/76) of patients receiving iodixanol-320 (95% confidence interval $-6.2, 1.0, P = 0.2$). A relative increase $\geq 25\%$ in SCr occurred in 4% (3/77) of patients receiving iopamidol-370 and in 4% (3/76) of the patients receiving iodixanol-320 (95% confidence interval $-6.2, 6.1, P = 1.0$).

Conclusion: The rate of CIN was similarly low in risk patients after intravenous administration of iopamidol-370 or iodixanol-320 for CE-MDCT.

Key Words: chronic kidney disease, contrast media, contrast-induced nephropathy, computed tomography

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The hypothesis that isotonic contrast media may have better renal tolerance in high-risk patients compared with low-osmolar contrast media has had considerable impact in the scientific community. It has even influenced the recommendations of several guidelines despite the fact it has only been shown in one single study.¹ Contrast-induced nephropathy (CIN) is an acute decline in renal function occurring after the intravascular administration of contrast media (CM) and in the absence of alternative etiology.¹⁻³ Most studies have defined CIN as a postcontrast increase from baseline in serum creatinine (SCr) of more than 25% or as an absolute increase of 0.5 mg/dL (44.2 $\mu\text{mol/L}$) above precontrast values.^{4,5} In most cases, the rise in SCr occurs within 24 to 48 hours of exposure to iodinated contrast media, with a return to baseline or near baseline within 7 days.³⁻⁶ A number of studies have evaluated the nephrotoxicity of the nonionic, dimeric agent iodixanol (Visipaque, Amersham Health Inc., Princeton, NJ), isotonic to human plasma, or that of other low-osmolal, nonionic, monomeric CM in patients with renal failure undergoing intra-arterial injections of CM.⁷⁻²⁹ Only 2 studies have compared the renal safety of iodixanol to nonionic monomeric CM after their intravenous administra-

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Investigators in the Isovue-370 and Visipaque-320 in renally impaired patients undergoing Computed Tomography (IMPACT) study are listed in the Appendix.

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tion.^{30,31} In both studies, the incidence of CIN after the intravenous injection of iodixanol and the comparator was almost superimposable. However, the sample size of these studies was too small to draw firm conclusions. The aim of the IMPACT (Isovue-370 and Visipaque-320 in renally *IM*paired *PAT*ients undergoing *Computed Tomography*) study was to prospectively compare the incidence of CIN after the intravenous injection of equi-iodine doses of iopamidol-370 (Isovue, Bracco Diagnostics Inc., Princeton, NJ, 370 mgI/mL, 796 mOsm per kg of water) and iodixanol-320 (320 mgI/mL, 290 mOsm per kg of water) in a larger cohort of patients with moderate-to-severe chronic kidney disease (stages 3 and 4 according to the classification of chronic kidney disease by the National Kidney Foundation)³² undergoing contrast-enhanced multidetector computed tomographic (CE-MDCT) examinations.

MATERIALS AND METHODS

The IMPACT study was a multicenter, double-blind, randomized, parallel group comparison of iopamidol-370 and iodixanol-320 for CE-MDCT imaging of the liver or MDCT angiography of the lower-extremity vasculature. The study was conducted according to Good Clinical Practice standards at 12 centers in North America and at 3 centers in the People's Republic of China (see Appendix). The protocol was approved by each participating center's Institutional Review Board. The study was performed in accordance with the Declaration of Helsinki (Helsinki, Finland, 1964) and subsequent amendments (Tokyo, Japan, 1975; Venice, Italy, 1983; Hong Kong, 1989; and Somerset West, Republic of South Africa, 1996). All patients gave written informed consent before enrollment in the study.

Study Patients

A total of 166 patients, 18 years of age or older, with chronic moderate-to-severe kidney disease (SCr ≥ 1.5 mg/dL [$133 \mu\text{mol/L}$] or CrCl between 10 and 59 mL/min) who were referred for a clinically indicated CE-MDCT examination of the liver or peripheral vasculature were enrolled in a consecutive manner at each center. Entry criteria were a SCr and calculated CrCl determination within 2 weeks before study drug administration that met the inclusion criteria and were consistent with a previous result obtained within 6 months before administration of CM. If a patient only had one SCr and or calculated CrCl determination within a 6-month period, the SCr measurement and CrCl calculation was repeated within the 72 hours before dosing. A patient's kidney disease was considered stable if the average daily variation between precontrast screening CrCl values was 1% or less.

Patients were ineligible for the study if they had received an investigational drug within 30 days before admission to the study, or had undergone or were scheduled to undergo any other radiologic procedure using radiographic contrast media from 72 hours before to 7 days after the administration of the study agent. Patients were also ineligible for the study if they had New York Heart Association Class III or IV congestive heart failure or other medical conditions or circumstances which would have substantially decreased the chances of obtaining reliable data (eg, hypersensitivity to iodine-containing compounds, hyperthyroidism

or thyroid malignancies, uncontrolled diabetes, unstable renal function, drug dependence, psychiatric disorders, dementia). Finally, nursing or pregnant patients were ineligible, as were patients scheduled to receive any medication to prevent CIN (eg, N-acetylcysteine, theophylline, fenoldopam or other drug). Volume supplementation was given according to clinical practice or protocols of each site for each patient in whom it was deemed clinically necessary or desirable.

Study Protocol

A computer-generated, balanced randomization scheme was provided to the clinical trial sites along with the drug accountability logs. Patients were assigned randomly to receive the intravenous injection of iopamidol-370 or iodixanol-320. The prespecified total iodine dose was 40 g of iodine (gI) for all patients administered at a standardized injection rate of 4 mL/s. All groups and individuals associated with the study remained blinded until the database was locked and the data analyzed. To ensure blinding at the investigational sites, a third-party blind (drug-dispensing person) managed the preparation, dispensing, and accountability of the investigational agents, as per code assignment. The drug-dispensing persons' sole responsibility was to preserve the blind and, therefore, they did not participate in any of the study assessments. After patient enrollment, blood samples for SCr and CrCl determination were obtained within 72 hours precontrast and at $48-72 \pm 6$ hours after contrast administration. Precontrast baseline samples were to be taken before any volume supplementation procedure was started. A central laboratory (Covance Central Laboratory Services, Indianapolis, IN) developed study-specific collection kits and performed the SCr measurements and CrCl calculations. SCr determinations were performed on a Roche Modular Analyzer using commercial reagents. The assay used was a substrate triggered, rate-blanked method, using a modification of the Jaffe reaction. CrCl was calculated using the Cockcroft-Gault formula.³³ A Renal Safety Data Monitoring Board, comprising 3 independent medical experts (B.J.B., R.W.K., H.S.T.), was established to determine that patients met study eligibility criteria, had stable kidney disease and were eligible to be included in the statistical analysis. The Renal Safety Data Monitoring Board reviewed the renal safety data (predose and postdose SCr and CrCl controls and values), and other necessary related data (eg, demographics, medical history, concomitant medications, volume supplementation, contrast dose) of each patient in a blinded manner. CIN was the primary end point, defined as an absolute increase ≥ 0.5 mg/dL [$44.2 \mu\text{mol/L}$] or a relative increase in SCr $\geq 25\%$ from baseline to $48-72 \pm 6$ hours after contrast.

Statistical Analysis

CIN was assessed in those patients who received 1 of the 2 randomized contrast agents, who had SCr measurements available before contrast and at $48-72 \pm 6$ hours after contrast, and whose eligibility was confirmed by the Renal Safety Data Monitoring Board. Age, weight, body mass index, volume of prophylactic fluids, total contrast iodine dose, contrast iodine dose per kg body weight, and iodine dose per unit of CrCl were summarized as mean \pm one standard deviation. Unpaired Stu-

dent *t* test was performed to determine differences between mean values for those continuous variables precontrast and postcontrast. After the confirmation of normal distribution, SCr and CrCl also were compared across groups before contrast by unpaired *t* test. Categorical variables (gender, race, presence or absence of diabetes mellitus, use of any volume supplementation, and concomitant nephrotoxic medications) were analyzed using a χ^2 test. Postcontrast changes in SCr were summarized as mean and one standard deviation. Mean changes in SCr also were tested for normality and analyzed using analysis of covariance (ANCOVA), with predose measurement as covariate. The incidence of CIN was analyzed using Fisher exact test, two-sided. Logistic regression analyses were performed, using SCr increases by 25% or more as the dependent variable, contrast agents as treatment groups along with risk factors such as age, gender, diabetes mellitus, volume supplementation, predose SCr or CrCl, total dose by body weight or by CrCl, intrinsic kidney diseases versus other reasons for reduced kidney function, hypertension, and concomitant use of potentially nephrotoxic medications as covariates. Probability values of <0.05 were considered to be significant. The statistical analysis was performed using SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS

Between November 2004 and November 2005, a total of 166 patients were enrolled at 15 study centers (range of patients enrolled per site, 1–31; median site enrollment, 8). Of the 166 patients enrolled in the study, 84 received iopamidol-370 and 82 iodixanol-320. A total of 153 subjects were considered evaluable by the Renal Safety Data Monitoring Board and were included in the final safety analysis. Thirteen patients (7 from the iopamidol-370 group and 6 from the iodixanol-320 group) were excluded from the analysis for the following reasons: 1 patient had no follow-up SCr measurement until 7 days after CM dose, 1 patient had preplanned hemodialysis, which took place immediately after the MDCT examination; 3 patients had less than the protocol-mandated screening SCr measurements; and 8 patients had an average precontrast daily CrCl variation greater than 1% (Fig. 1). The 13 patients excluded from the statistical analysis received the same iodine dose (40 gI). Their mean SCr values remained almost unchanged after contrast administration (from 1.61 ± 1.09 to 1.57 ± 0.87 mg/dL after iopamidol-370, from 1.25 ± 0.30 to 1.28 ± 0.26 mg/dL after iodixanol-320), and none of them experienced CIN, by any measure used.

Of the 153 evaluable patients, 77 received iopamidol-370 and 76 received iodixanol-320. The demographic, clinical, procedural and biochemical characteristics of the 153 patients in the 2 groups are presented in Table 1. Evaluable patients had SCr measurements and CrCl calculations performed precontrast and SCr measurements at 48 to 72 \pm 6 hours postcontrast (mean, 57.4 hours). The 2 study groups were comparable with regard to mean age, gender distribution, presence of diabetes or hypertension, concomitant nephrotoxic medications, volume supplementation, iodine dose, iodine dose per kg body weight, and iodine dose per unit of CrCl. Periprocedural volume supplementation was performed in 64% of the iopamidol-370 patients and in 66% of the iodixanol-320 patients. The total amount of intravenous volume

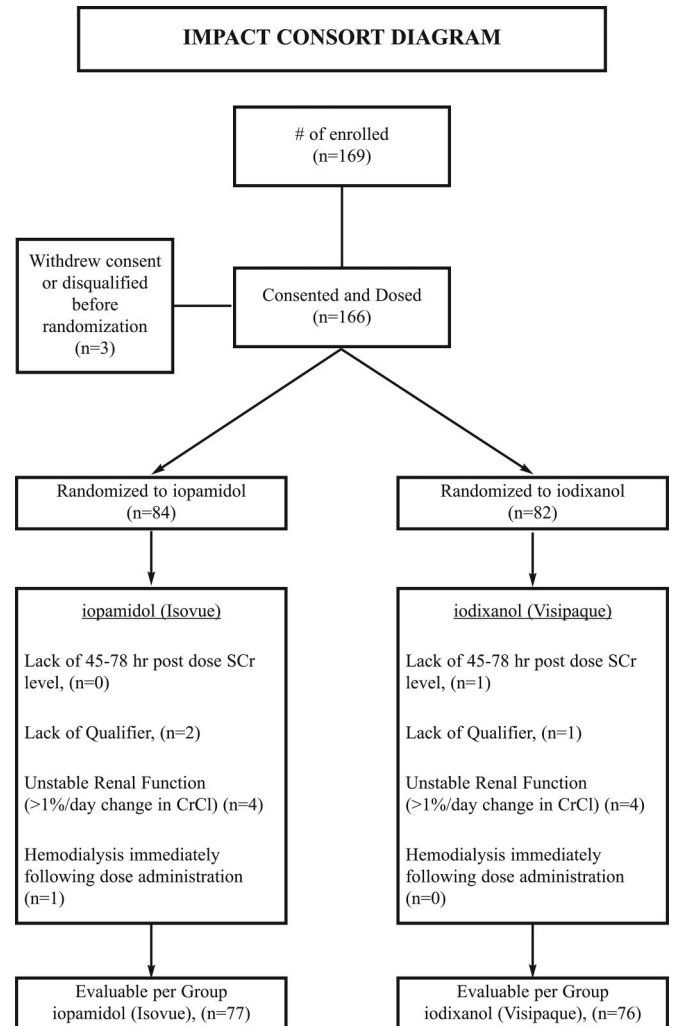


FIGURE 1. Disposition of subjects in the IMPACT trial.

supplementation was comparable in the 2 groups, as was the number of subjects receiving bicarbonate hydration. Precontrast SCr was 1.6 ± 0.4 mg/dL in both groups ($P = 0.9$). Predose CrCl was 44.1 ± 14.0 mL/min in the iopamidol-370 group and 45.2 ± 11.3 mL/min in the iodixanol-320 group ($P = 0.6$).

Contrast-Induced Nephropathy

Table 2 describes the incidence of CIN in the 2 study groups. An absolute increase ≥ 0.5 mg/dL ($44.2 \mu\text{mol/L}$) in SCr was observed in 2.6% (2/76) of patients in the iodixanol-320 group and in no patients in the iopamidol-370 group (95% CI $[-6.2\%, 1.0\%]$, $P = 0.2$). Both patients experiencing CIN after iodixanol-320 were nondiabetic and received prophylactic volume supplementation. A relative $\geq 25\%$ increase in SCr occurred in 4.0% (3/76) of the patients receiving iodixanol-320 and in 3.9% (3/77) of the patients receiving iopamidol-370 (95% CI $[-6.2\%, 6.1\%]$, $P = 1.0$). Only one of the 6 patients experiencing a $\geq 25\%$ relative increase in SCr was diabetic. A total of 18 patients had a baseline SCr ≥ 2.0 mg/dL ($\geq 177 \mu\text{mol/L}$), 11 in the iopamidol-370 group and 7 in the iodixanol-320 group. In this subset of patients at

TABLE 1. Clinical, Biochemical, and Procedural Characteristics of Study Patients

Characteristic	Iopamidol-370 Group (n = 77)	Iodixanol-320 Group (n = 76)	P
Mean age, years	67.3 ± 13.0	67.0 ± 11.5	0.90
Gender, M/F	54/23	51/25	0.69
Race			0.19
White (%)	42 (54.6)	43 (56.6)	
Black (%)	8 (10.4)	4 (5.3)	
Asian (%)	24 (31.2)	29 (38.2)	
Other (%)	3 (3.9)	0	
Mean body weight, kg	70.9 ± 17.4	72.7 ± 17.5	0.53
Mean body mass index, kg/m ²	25.1 ± 5.1	25.7 ± 5.4	0.46
Diabetes mellitus (%)	15 (19.5)	21 (27.6)	0.23
Hypertension (%)	56 (72.7)	56 (73.7)	0.89
Concomitant nephrotoxic medications (%)	9 (11.7)	4 (5.3)	0.32
Mean baseline serum creatinine, mg/dL	1.6 ± 0.4	1.5 ± 0.5	0.70
Mean baseline creatinine clearance, mL/min	44.1 ± 14.0	45.2 ± 11.3	0.60
Hydration performed, n (%)	49 (64)	50 (66)	0.78
Mean volume of intravenous hydration, mL	552 ± 497	644 ± 646	0.43
Mean total dose of contrast, gI	40.4 ± 2.5	40.0 ± 1.3	0.24
Mean dose (gI)/body weight, kg	0.6 ± 0.1	0.6 ± 0.1	0.41
Mean dose (gI)/creatinine clearance, mL/min	1.0 ± 0.4	0.9 ± 0.3	0.14

Mean data presented as mean ± standard deviation.
Categorical data presented as n (%).
For the comparison of continuous variables, *t* test was used. For categorical variables, χ^2 test was applied.

TABLE 2. Postdose Changes in Serum Creatinine

Variable	Iopamidol-370 Group	Iodixanol-320 Group	Iopamidol Group minus Iodixanol Group (95% Confidence Interval)	P*
Serum creatinine (mg/dL)				
Baseline	1.6 ± 0.4	1.5 ± 0.5	0.03 (-0.11, 0.17)	0.7
Postdose	1.6 ± 0.4	1.6 ± 0.5	-0.01 (-0.16, 0.13)	0.9
Change from baseline	0.00 ± 0.16	0.04 ± 0.24	-0.04 (-0.11, 0.02)	0.2
Contrast-induced nephropathy				
Postcontrast increase in serum creatinine				
≥0.5 mg/dL	0	2 (2.6%)	-2.6 (-6.2, 1.0)	0.3
≥25%	3 (3.9%)	3 (4.0%)	0 (-6.2, 6.1)	0.4

*For the comparison of SCr at baseline and 48–72 hours post-dose, *t* test was used. For change in SCr, ANCOVA was applied by treating baseline measurement as covariate. For categorical variables, Fisher exact test was applied.

higher risk, CIN was observed in 2 patients following the administration of iodixanol-320 and in none of the patients administered iopamidol-370. No case of acute deterioration of renal function requiring dialysis or hospitalization was observed in this trial.

Logistic regression analyses were performed by treating CIN (≥25% postcontrast increase in SCr) as the dependent variable, and contrast group along with risk factors as independent variables. The results failed to show any significant relationship between the occurrence of CIN and age, gender, race, diabetes mellitus, dose by body weight, baseline creatinine clearance, intrinsic kidney diseases versus other reasons for reduced kidney function, hypertension, and use of concomitant potentially nephrotoxic medications. No significant treatment effect was evident between the 2 contrast

agent groups. Volume supplementation was the only significant factor in reducing the incidence of CIN.

DISCUSSION

The results of this trial failed to demonstrate any difference in the incidence of CIN between equi-iodine doses of the nonionic dimer iodixanol-320, isotonic to human plasma, and the nonionic monomer iopamidol-370, hypersomolal to human plasma, for intravenous use in patients with pre-existing stable chronically reduced kidney function. This is at odds with the findings of a previous trial comparing another nonionic monomer, iohexol (Omnipaque, GE Healthcare Inc., Princeton, NJ) with the nonionic dimer iodixanol,⁹ but consistent with the findings in other prospective^{10,30,31} or

retrospective studies.²⁹ Most of the studies comparing the nephrotoxicity of the nonionic dimer iodixanol to nonionic monomers have been in patients having intra-arterial injections either to the heart or the peripheral arteries.^{9,10,29} Although the relative nephrotoxicity of individual low-osmolal, nonionic monomers has not been established by head to head comparisons among them, the reported rates of CIN were higher with iohexol than with iopamidol in 3 recent pooled analyses of clinical studies.^{34–36} Several previous studies comparing the nephrotoxicity of the nonionic dimer iodixanol and nonionic monomers have weaknesses that detract from our ability to reach valid conclusions. Either the studies were not prospective,²⁹ not blinded,¹⁰ the timing of outcome assessment was unclear,¹⁰ the trial was only reported in abstract form,³¹ or the sample size was small.^{30,31}

The IMPACT study is the largest, prospective, randomized, double-blind comparison of the dimer iodixanol with a nonionic monomer. Patients in this trial had SCr measurements performed between 2 and 3 days postcontrast in a central laboratory. The incidence of CIN was low overall (3.9–4% when a relative rise in SCr $\geq 25\%$ from baseline was taken as CIN end point), despite the fact that patients did not receive medications to prevent contrast nephrotoxicity and only approximately 65% of patients received some form of fluid prophylaxis. Similarly to the NEPHRIC study,⁹ the dose, route of administration, and duration of volume supplementation varied widely, because these values were left to investigator discretion. Use of prophylactic hydration was identified as a protective factor in our multivariate analysis, whereas no significant relationship was observed between the occurrence of CIN and age, gender, race, diabetes mellitus, dose by body weight, baseline CrCl, intrinsic kidney diseases versus other reasons for reduced kidney function, hypertension, and use of concomitant potentially nephrotoxic medications.

The relatively low incidence of CIN observed in the IMPACT study is consistent with some,^{30,37} but not all studies of low-osmolal contrast given intravenously to patients with chronic kidney disease.^{31,38–40} Carraro et al reported no cases of CIN following iopromide and a CIN rate of 3.1% following iodixanol in patients with pre-existing chronic kidney disease (baseline SCr averaging 1.6 mg/dL, 150 $\mu\text{mol/L}$) undergoing intravenous excretory urography at an average iodine dose of 45 gI/patient.³⁰ Garcia-Ruiz et al reported on 50 cases with baseline CrCl averaging 29.8 mL/min having CT angiography with iopromide at an average iodine dose of 48 gI/patient.³⁷ No intravenous volume supplementation was used, but patients were encouraged to drink one liter of water 12 hours before and 2 L in the 24 hours after the procedure. Serum creatinine increased by more than 20% within 72 hours in 2 cases (4%). In a prospective study by Becker and Reiser³⁸ involving 100 consecutive cases with baseline estimated glomerular filtration rate averaging 37 mL/min/1.73 m², given 27 gI as iodixanol intravenously for CT angiography, 9% of patients demonstrated an increase in SCr of greater than 0.5 mg/dL (44 $\mu\text{mol/L}$) by day three. Lufft et al³⁹ reported a similar incidence of 9% for CIN in 33 patients with renal impairment

having CT angiography with a 45 gI dose/patient of iopentol using 0.45% saline prophylaxis. Two other studies reported a higher rate of CIN (17–21%) with nonionic monomers or with the nonionic dimer, but the patients in these studies had a more severe pre-existing degree of renal impairment.^{31,40}

The true cause of acute renal failure after contrast is difficult to determine clinically, particularly in populations having cardiac angiography, where hemodynamic instability, atheroembolism and the effects of other drugs may all play a role.³ To that extent, studies comparing agents given intravenously may be less prone to confounding by causes of kidney failure other than CIN. However, it also must be noted that small and transient changes in kidney function have been documented in a proportion of cases having CT examinations without contrast and control groups not exposed to contrast can be helpful in judging the true nephrotoxic potential of a contrast agent.^{41–43}

It has been suggested that the nephrotoxicity of contrast media is a function of dose in relation to level of kidney function at the time of injection.^{44,45} The dose of contrast by necessity varies between patients undergoing cardiac angiography with and without stent placement, and the similarity of trial groups in terms of individual patient dose per unit of kidney function is generally not reported. This is more of an issue when interpreting data from trials with relatively small numbers of subjects per group, where an unreported imbalance might significantly affect the results. Moreover, the dose of contrast is usually reported as injected volume, even if the iodine strength of contrast solutions could vary from 140 mgI/mL up to 400 mgI/mL. The protocol for the current study called for a fixed and equi-iodine dose of contrast to be given to all participants. This helped reduce the potential influence of another important parameter in comparing contrast agent nephrotoxicity, as variability between subjects then derives only from body size or level of kidney function. In the current study the total dose in terms of grams iodine was equivalent between study groups. Iodine dose/kg body weight and iodine dose/per unit of CrCl were also equivalently distributed in the 2 study groups.

Most previous trials have not been as rigorous in determining the stability of kidney function among trial participants before contrast administration. It is clearly difficult to say whether CIN is responsible for a decline in kidney function in patients with changing kidney function before contrast. The definition of “stable” kidney function in this study was based on a review of trial data before unblinding. Because the qualifying SCr levels were drawn at various points in the days to months prior to the study, we used an average change in kidney function of less than one percent per day (in either direction) as our criterion for clinical stability.

Study Limitations

There are a few limitations to the current study. Thirteen patients (7.8%) were determined to be ineligible after study completion and were not included in the primary analysis. However, their eligibility was determined before unblinding and analysis by trial group and importantly, none of these cases met the criteria for CIN. As mentioned previ-

ously, the use of prophylactic hydration was not uniform, but was balanced across trial groups. The sample size of the study was calculated based on the apparent differences between contrast agents in the NEPHRIC study.⁹ While the number of subjects reported here is higher than that in the NEPHRIC study (153 vs. 129), the incidence of CIN observed was lower than anticipated in planning this trial. However, the 95% confidence interval around the difference in incidence of a 0.5 mg/L increase in SCr seen between trial groups ranges from -6.2% to 1.0%. Thus, our results are compatible with an absolute difference in CIN rates of close to 6% in favor of iopamidol or 1% in favor of iodixanol. With the CIN incidence rates seen in the current trial, a study of about 3800 cases would be required to detect even a 50% reduction in the incidence of CIN with one contrast medium over the other.

CONCLUSIONS

The rate of CIN in patients with moderate-to-severe chronic kidney disease was similarly low after the intravenous administration of 40 gI of iopamidol-370 or iodixanol-320 for contrast-enhanced multidetector CT.

REFERENCES

- Morcos SK, Thomsen HS, Webb JA. Contrast-media-induced nephrotoxicity: a consensus report. Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR). *Eur Radiol.* 1999;9:1602-1613.
- Thomsen HS, Morcos SK. Contrast media and the kidney: European Society of Urogenital Radiology (ESUR) guidelines. *Br J Radiol.* 2003;76:513-518.
- Barrett BJ, Parfrey PS. Preventing nephropathy induced by contrast medium. *N Engl J Med.* 2006;354:379-386.
- McCullough PA, Sandberg KR. Epidemiology of contrast-induced nephropathy. *Rev Cardiovasc Med.* 2003;4(Suppl 5):S3-S9.
- Thomsen HS. Guidelines for contrast media from the European Society of Urogenital Radiology. *AJR Am J Roentgenol.* 2003;181:1463-1471.
- Murphy SW, Barrett BJ, Parfrey PS. Contrast nephropathy. *J Am Soc Nephrol.* 2000;11:177-182.
- Taliercio CP, Vlietstra RE, Ilstrup DM, et al. A randomized comparison of nephrotoxicity of iopamidol and diatrizoate in high risk patients undergoing cardiac angiography. *J Am Col Cardiol.* 1991;17:384-390.
- 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.
- Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med.* 2003;348:491-499.
- Chalmers N, Jackson RW. Comparison of iodixanol and iohexol in renal impairment. *Br J Radiol.* 1999;72:701-703.
- Durham JD, Caputo C, Dokko J, et al. A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. *Kidney Int.* 2002;2:2202-2207.
- Hans SS, Hans BA, Dhillon R, et al. Effect of dopamine on renal function after arteriography in patients with pre-existing renal insufficiency. *Am Surg.* 1998;64:432-436.
- Miner SE, Dzavik V, Nguyen-Ho P, et al. N-acetylcysteine reduces contrast-associated nephropathy but not clinical events during long-term follow-up. *Am Heart J.* 2004;148:690-695.
- Baker CS, Wragg A, Kumar S, et al. A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. *J Am Col Cardiol.* 2003;41:2114-2118.
- Boccalandro F, Amhad M, Smalling RW, et al. Oral acetylcysteine does not protect renal function from moderate to high doses of intravenous radiographic contrast. *Catheter Cardiovasc Interv.* 2003;58:336-341.
- Briguori C, Colombo A, Airolidi F, et al. N-acetylcysteine versus fenoldopam mesylate to prevent contrast agent-associated nephrotoxicity. *J Am Coll Cardiol.* 2004;44:762-765.
- Shyu K-G, Cheng J-J, Kuan P. Acetylcysteine protects against renal damage in patients with abnormal renal function undergoing a coronary procedure. *J Am Coll Cardiol.* 2002;40:1383-1388.
- Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention. *JAMA.* 2003;289:553-558.
- Oldemeyer JB, Biddle WP, Wurdeman RL, et al. Acetylcysteine in the prevention of contrast-induced nephropathy after coronary angiography. *Am Heart J.* 2003;146:e23.
- Goldenberg I, Shechter M, Matetzky S, et al. Oral acetylcysteine as an adjunct to saline hydration for the prevention of contrast-induced nephropathy following coronary angiography: a randomized controlled trial and review of the current literature. *Eur Heart J.* 2004;25:212-218.
- Huber W, Schiepek C, Ilgmann K, et al. Effectiveness of theophylline prophylaxis of renal impairment after coronary angiography in patients with chronic renal insufficiency. *Am J Cardiol.* 2003;91:1157-1162.
- Briguori C, Manganeli F, Scarpato P, et al. Acetylcysteine and contrast agent-associated nephrotoxicity. *J Am Col Cardiol.* 2002;40:298-303.
- Fung JW, Szeto CC, Chan WW, et al. Effect of N-acetylcysteine for prevention of contrast nephropathy in patients with moderate to severe renal insufficiency: a randomized trial. *Am J Kidney Dis.* 2004;43:801-808.
- Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). *Am J Cardiol.* 2002;89:356-358.
- Marenzi G, Marana I, Lauri G, et al. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med.* 2003;349:1333-1340.
- Webb JG, Pate GE, Humphries KH, et al. A randomized controlled trial of intravenous N-acetylcysteine for the prevention of contrast-induced nephropathy after cardiac catheterization: lack of effect. *Am Heart J.* 2004;148:422-429.
- Abizaid AS, Clark CE, Mintz GS, et al. Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. *Am J Cardiol.* 1999;83:260-263.
- Briguori C, Colombo A, Violante A, et al. Standard vs double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity. *Eur Heart J.* 2004;25:206-211.
- Briguori C, Colombo A, Airolidi F, et al. Nephrotoxicity of low-osmolality versus iso-osmolality contrast agents: impact of N-acetylcysteine. *Kidney Int.* 2005;68:2250-2255.
- Carraro M, Malalan F, Antonione R, et al. Effects of a dimeric vs. a monomeric nonionic contrast medium on renal function in patients with mild to moderate renal insufficiency: a double-blind, randomized clinical trial. *Eur Radiol.* 1998;8:144-147.
- Kolehmainen H, Soiva M. Comparison of Xenetix 300 and Visipaque 320 in patients with renal failure. *Eur Radiol.* 2003;13:B32-B33.
- National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39:S1-S266.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31-41.
- Solomon R. The role of osmolality in the incidence of contrast-induced nephropathy: a systematic review of angiographic contrast media in high risk patients. *Kidney Int.* 2005;68:2256-2263.
- Sharma S, Kini A. Effect of nonionic radiocontrast agents on the occurrence of contrast-induced nephropathy in patients with mild-moderate chronic renal insufficiency: pooled analysis of the randomized trials. *Catheter Cardiovasc Interv.* 2005;65:386-393.
- Solomon R, DuMouchel W. Contrast media and nephropathy: findings from systematic analysis and Food and Drug Administration reports of adverse effects. *Invest Radiol.* 2006;41:651-660.
- Garcia-Ruiz C, Martinez-Vea A, Sempere T, et al. Low risk of contrast nephropathy in high-risk patients undergoing spiral computed tomography angiography with the contrast medium iopromide and prophylactic oral hydration. *Clin Nephrol.* 2004;61:170-176.
- Becker CR, Reiser MF. Use of iso-osmolar nonionic dimeric contrast

- media in multidetector row computed tomography angiography for patients with renal impairment. *Invest Radiol.* 2005;40:672–675.
39. Lufft V, Hoogestraat-Lufft L, Fels LM, et al. Contrast media nephropathy: intravenous CT angiography versus intraarterial digital subtraction angiography in renal artery stenosis: a prospective randomized trial. *Am J Kidney Dis.* 2002;40:236–242.
 40. 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.
 41. Cramer BC, Parfrey PS, Hutchinson TA, et al. Renal function following infusion of radiologic contrast material: a prospective controlled study. *Arch Intern Med.* 1985;145:87–89.
 42. Heller CA, Knapp J, Halliday J, et al. Failure to demonstrate contrast nephrotoxicity. *Med J Aust.* 1991;155:329–332.
 43. Rao QA, Newhouse JH. Risk of nephropathy after intravenous administration of contrast material: a critical literature analysis. *Radiology.* 2006;239:393–397.
 44. Cigarroa RG, Lange RA, Williams RH, et al. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. *Am J Med.* 1989;86:649–652.
 45. Freeman RV, O'Donnell M, Share D, et al. Nephropathy requiring dialysis after percutaneous coronary intervention and the critical role of an adjusted contrast dose. *Am J Cardiol.* 2002;90:1068–1073.

APPENDIX

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