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# Cardiac Angiography in Renally Impaired Patients (CARE) Study

## A Randomized Double-Blind Trial of Contrast-Induced Nephropathy in Patients With Chronic Kidney Disease

Richard J. Solomon, MD; Madhu K. Natarajan, MD; Serge Doucet, MD; Samin K. Sharma, MD; Cezar S. Staniloae, MD; Richard E. Katholi, MD; Joseph L. Gelormini, MD; Marino Labinaz, MD; Abel E. Moreyra, MD; the Investigators of the CARE Study

**Background**—No direct comparisons exist of the renal tolerability of the low-osmolality contrast medium iopamidol with that of the iso-osmolality contrast medium iodixanol in high-risk patients.

**Methods and Results**—The present study is a multicenter, randomized, double-blind comparison of iopamidol and iodixanol in patients with chronic kidney disease (estimated glomerular filtration rate, 20 to 59 mL/min) who underwent cardiac angiography or percutaneous coronary interventions. Serum creatinine (SCr) levels and estimated glomerular filtration rate were assessed at baseline and 2 to 5 days after receiving medications. The primary outcome was a postdose SCr increase  $\geq 0.5$  mg/dL (44.2  $\mu\text{mol/L}$ ) over baseline. Secondary outcomes were a postdose SCr increase  $\geq 25\%$ , a postdose estimated glomerular filtration rate decrease of  $\geq 25\%$ , and the mean peak change in SCr. In 414 patients, contrast volume, presence of diabetes mellitus, use of N-acetylcysteine, mean baseline SCr, and estimated glomerular filtration rate were comparable in the 2 groups. SCr increases  $\geq 0.5$  mg/dL occurred in 4.4% (9 of 204 patients) after iopamidol and 6.7% (14 of 210 patients) after iodixanol ( $P=0.39$ ), whereas rates of SCr increases  $\geq 25\%$  were 9.8% and 12.4%, respectively ( $P=0.44$ ). In patients with diabetes, SCr increases  $\geq 0.5$  mg/dL were 5.1% (4 of 78 patients) with iopamidol and 13.0% (12 of 92 patients) with iodixanol ( $P=0.11$ ), whereas SCr increases  $\geq 25\%$  were 10.3% and 15.2%, respectively ( $P=0.37$ ). Mean post-SCr increases were significantly less with iopamidol (all patients: 0.07 versus 0.12 mg/dL, 6.2 versus 10.6  $\mu\text{mol/L}$ ,  $P=0.03$ ; patients with diabetes: 0.07 versus 0.16 mg/dL, 6.2 versus 14.1  $\mu\text{mol/L}$ ,  $P=0.01$ ).

**Conclusions**—The rate of contrast-induced nephropathy, defined by multiple end points, is not statistically different after the intraarterial administration of iopamidol or iodixanol to high-risk patients, with or without diabetes mellitus. Any true difference between the agents is small and not likely to be clinically significant. (*Circulation*. 2007;115:3189-3196.)

**Key Words:** contrast media ■ diabetic nephropathy ■ iodixanol ■ iopamidol ■ kidney

The number of cardiac angiography and percutaneous coronary interventions has increased steadily in recent years.<sup>1</sup> This has resulted in the increasing incidence of contrast-induced nephropathy (CIN), an acute impairment of renal function that occurs after the administration of the contrast media (CM) and that is responsible for  $\approx 11\%$  of cases of hospital-acquired renal insufficiency.<sup>2</sup> Moderate to severe chronic kidney disease (CKD), defined as estimated glomerular filtration rate (eGFR)  $< 60$  mL/min per 1.73 m<sup>2</sup> (National Kidney Foundation, CKD stages 3 and 4)<sup>3</sup> is the most important risk factor for the development of CIN.<sup>4</sup> Other major risk factors for CIN include older age, diabetes melli-

tus, intraarterial CM administration, use of large CM doses, the concurrent use of nephrotoxic drugs, patient dehydration, and any other condition associated with decreased effective

### Clinical Perspective p 3196

circulating volume.<sup>5-7</sup> As for the individual propensities of the various CM to cause CIN, a small-scale study (the Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media [NEPHRIC] study)<sup>8</sup> showed that the nonionic dimer iodixanol-320 (290 mOsm/kg), isotonic to human plasma, was less nephrotoxic than the nonionic monomer iohexol-350 (844 mOsm/kg) in cardiac and peripheral

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From the Department of Renal Services (R.J.S.), Fletcher Allen Health Care, Burlington, Vt.; Division of Cardiology (M.K.N.), Hamilton Health Sciences General Division, Hamilton, Ontario, Canada; Department of Medicine (S.D.), Montreal Heart Institute, University of Montreal, Quebec, Canada; Cardiovascular Institute (S.K.S.), Mount Sinai Medical Center, New York, NY; Comprehensive Cardiovascular Center (C.S.S.), St. Vincent's Medical Center Manhattan, New York, NY; Department of Medicine (R.E.K.), Southern Illinois University, Springfield; Interventional Cardiology (J.L.G.), Buffalo Heart Group, Buffalo, NY; Department of Medicine (M.L.), Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada; Department of Medicine (A.E.M.), Division of Cardiology, Robert Wood Johnson Medical School, New Brunswick, NJ.

Correspondence to Richard J. Solomon, MD, Fletcher Allen Health Care, University of Vermont, UHC 2309, 1 South Prospect St, Burlington, VT 05401. E-mail richard.solomon@vtmednet.org

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angiography in 129 patients with diabetes mellitus and CKD. Several other studies compared the nephrotoxicity of the non-ionic dimer iodixanol and nonionic monomers in renally impaired patients, but all of them had limitations that prevent valid conclusions. Either the studies were not prospective<sup>9</sup> or were not blinded,<sup>10</sup> the timing of outcome assessment was unclear,<sup>10</sup> the number of evaluable patients was small,<sup>10,11</sup> or the patients received the CM intravenously.<sup>11</sup> More recently, a single-center trial, the RECOVER study, compared iodixanol to a low-osmolality but ionic CM, ioxaglate, in CKD patients and found no difference in the incidence of CIN defined as an absolute SCr increase  $\geq 0.5$  mg/dL from baseline.<sup>12</sup>

The present study (the Cardiac Angiography in Renally Impaired Patients [CARE] study) aimed to provide a prospective, multicenter, randomized, double-blind comparison of the incidence of CIN between the nonionic monomer iopamidol-370 (Isovue 370, Bracco Diagnostics Inc, Princeton, NJ; 796 mOsm/kg) and the nonionic dimer iodixanol-320 (Visipaque 320, GE Healthcare, Princeton, NJ; 290 mOsm/kg) after their intraarterial administration to patients with moderate to severe CKD who underwent diagnostic or interventional cardiac catheterization procedures.

## Methods

The CARE study was a multicenter, randomized, double-blind, parallel-group comparison of iopamidol-370 and iodixanol-320 conducted at 25 centers in North America between July 2005 and June 2006. The study was approved by the Institutional Review Board of each participating center and performed according to Good Clinical Practice standards and the principles of the Declaration of Helsinki and its subsequent amendments. Written informed consent was provided by all patients before enrollment in the study.

## Patient Population

For the present study, moderate to severe CKD was defined as an eGFR 20 to 59 mL/min per 1.73 m<sup>2</sup>, calculated via the abbreviated Modification of Diet in Renal Disease (MDRD) study equation<sup>13</sup> from SCr obtained within 72 hours of enrollment. Men and women aged 18 years and older who were scheduled to undergo diagnostic cardiac angiography or percutaneous coronary interventions with moderate to severe CKD<sup>3</sup> were considered to be eligible. Criteria for exclusion were pregnancy, lactation, administration of any investigational drug within the previous 30 days, intraarterial or intravenous administration of iodinated CM from 7 days before to 72 hours after the administration of the study agents, medical conditions or circumstances that would have substantially decreased the chances to obtain reliable data (New York Heart Association class IV congestive heart failure, hypersensitivity to iodine-containing compounds, hyperthyroidism or thyroid malignancies, uncontrolled diabetes mellitus, unstable renal function, drug dependence, psychiatric disorders, dementia), administration of any medication to prevent CIN other than N-acetylcysteine (NAC), or intake of nephrotoxic medications from 24 hours before to 24 hours after the administration of the study agent.

## Study Conduct

A computer-generated balanced randomization scheme was provided to the study centers along with drug accountability logs. Patients were randomly assigned to receive the intraarterial administration of iopamidol-370 or iodixanol-320 as part of their scheduled cardiac catheterization procedure. 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 (person who dispensed the drugs) managed the preparation, dispensation, and accountability of the investigational agents, as per code assignment. The sole responsibility of each

person who dispensed the drugs was to preserve the blind; therefore, they did not participate in any of the study assessments.

All patients received prophylactic volume expansion with isotonic sodium bicarbonate solution, administered at 3 mL/kg per hr for 1 hour before angiography, and at 1 mL/kg per hr during angiography and for 6 hours after angiography. Each site chose whether they would administer a prophylactic NAC regimen to all of its patients, a regimen that consisted of an oral dose of 1200 mg twice per day administered on the day before and the day of the study procedure. The cardiac catheterization procedures and interventions were performed according to practice standards at the study sites. Study agent was administered by intraarterial injection as necessary for each patient, and the total CM volume administered was recorded.

Blood samples for baseline SCr and eGFR determination were obtained before the volume expansion procedure was started. SCr and eGFR determination were obtained again at 45 to 120 hours postdose and repeated on day 7 if a  $\geq 0.5$  mg/dL SCr increase was observed. A central laboratory (Covance Central Laboratory Services, Indianapolis, Ind) developed study-specific collection kits, performed all of the baseline and postdose SCr measurements, and calculated eGFR with the MDRD study equation.

## End Points

The primary CIN end point was defined as an absolute increase in SCr  $\geq 0.5$  mg/dL ( $\geq 44.2$   $\mu\text{mol/L}$ ) from baseline to 45 to 120 hours after study agent administration. Secondary CIN end points were the incidence of a  $\geq 25\%$  increase in SCr, a  $\geq 25\%$  decrease in eGFR from baseline, mean postdose increases in SCr, and the proportion of patients who required specific treatment for acute renal failure, hospitalization, dialysis, and deaths that occurred from acute renal failure.

## Statistical Analysis

Sample size calculation was based on the estimation of differences in CIN incidence rates between contrast agent groups by use of the 2-sided Fisher exact test, with type I error at 5% and 80% power. On the assumption that CIN rates in 1 group ranged from 5% to 15%<sup>14</sup> (200 patients in each group), a difference in absolute CIN incidence rates that ranged from 8.5% to 11.9% could be detected. For example, on the assumption that the observed CIN rate in 1 group is 5%, a difference of 8.5% or more could be detected (second agent CIN rate of 13.5%). Similarly, on the assumption that the CIN incidence rate in 1 group is 9.5%, a difference of 10.4% or more could be detected. In total, 480 patients were scheduled to be enrolled to account for dropouts or nonevaluable patients.

All data are presented as percentages or as mean  $\pm$  SD. The comparisons of baseline data between the 2 treatment groups were performed using the  $\chi^2$  test or Fisher exact test (categorical variables) and the Student *t* test (continuous variables).

Eligibility for CIN analysis was prospectively defined to include patients who received randomized contrast, underwent only 1 cardiac catheterization procedure during the study period, had SCr measurements at baseline and at 45 to 120 hours postdose, and did not have protocol violations. Protocol violations were defined as failure to meet inclusion criteria, meeting exclusion criteria, multiple angiographic procedures during the study period, no cardiac catheterization after randomization, other CM in addition to the randomized study agent, and/or a critical clinical event during the postdose follow-up period. Critical clinical events were defined as those that had a high likelihood to independently compromise renal function (eg, cardiac arrest, acute myocardial infarction, cardiovascular collapse, shock, or major surgery such as coronary artery bypass graft surgery). The evaluation of each patient's eligibility was completed by experienced physicians who did not participate in any of the study assessments before the blind was broken.

The difference in the incidence of CIN was analyzed with Fisher exact test. Diabetes mellitus was prespecified for subgroup analysis and inclusion in the multivariate logistic regression model.

Because the distributions of SCr concentrations and eGFR values were heavy-tailed, a natural logarithmic transformation of pre- and

postdose SCr and eGFR data were performed before analysis. An ANCOVA model was used to assess the difference in peak changes in SCr and eGFR between the CM groups, with the corresponding predose value as a covariate. In addition, to evaluate the effect of contrast agents on renal function, multivariate logistic regression analyses were performed with use of absolute ( $\geq 0.5$  mg/dL) or relative ( $\geq 25\%$ ) critical shifts in SCr as dependent variables. Contrast agents were used as treatment groups, along with risk factors such as age, gender, diabetes mellitus, volume supplementation, predose SCr or eGFR, total administered dose of volume and iodine (or by body weight), prophylactic medication use, and concomitant use of potentially nephrotoxic medications as covariates. All probability values  $< 0.05$  were considered to be statistically significant. The statistical analysis was performed with SAS version 8.2 (SAS Institute, Inc., Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

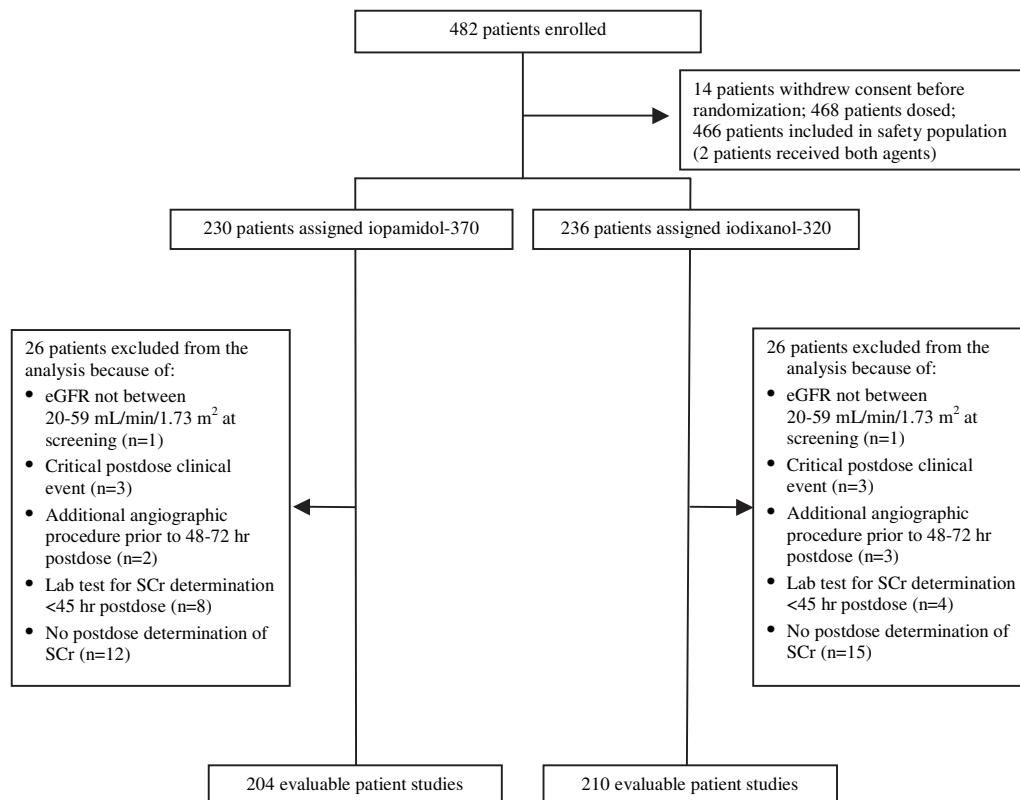
## Results

A total of 482 patients were enrolled (median number per center, 12; range, 2 to 66). Fourteen patients withdrew consent before assignment of a randomized contrast agent, and 2 patients mistakenly received both study agents, so that 466 patients were dosed with 1 randomized study agent as per protocol. Of these, 414 patients were evaluable for CIN analysis, whereas 52 patients (11%, 26 patients per treatment group) were excluded for a variety of reasons (Figure 1). Of these 52 patients, 27 patients (12 in the iopamidol-370 group and 15 in the iodixanol-320 group) had no postdose determination of SCr. Among the remaining 25 patients excluded for various protocol violations, 6 of them had postdose SCr elevations that would have met the criteria for CIN (4 in the iodixanol-320 group and 2 in the iopamidol-370 group).

## Comparability of Study Groups

Of the 414 evaluable patients, 204 received iopamidol-370 and 210 received iodixanol-320. The demographic, clinical, and procedural characteristics of patients in the 2 groups are presented in Table 1. The 2 study groups were comparable with regard to gender and race distribution, contrast volume, presence of diabetes mellitus, volume supplementation by body weight, time of postdose sampling, distribution by type of procedure (diagnostic cardiac angiography or percutaneous coronary intervention), and use of NAC. Patients who received iopamidol-370 were significantly older and received a significantly larger iodine dose per kg body weight.

The predose biochemical characteristics of the study groups are reported in Table 2. The baseline SCr was comparable between the 2 groups:  $1.46 \pm 0.36$  mg/dL in the iopamidol-370 group and  $1.44 \pm 0.41$  mg/dL in the iodixanol-320 group ( $P=0.64$ ). Baseline eGFR was also comparable between the 2 groups:  $49.3 \pm 11.6$  mL/min per  $1.73 \text{ m}^2$  in the iopamidol-370 group and  $50.2 \pm 13.0$  mL/min per  $1.73 \text{ m}^2$  in the iodixanol-320 group ( $P=0.45$ ). Baseline SCr and eGFR values were also comparable. The distribution of patients by degree of renal impairment was also not statistically different. The observation that these patients with moderately elevated SCr values had significant renal impairment (by MDRD) is probably related to their older age. This reinforces the current National Kidney Foundation recommendations that calculation of GFR from the SCr be the standard of care.<sup>3</sup>



Flow chart of trial progress.



**TABLE 1. Clinical and Procedural Characteristics of Study Patients**

Characteristic	Iopamidol-370 Group (n=204)	Iodixanol-320 Group (n=210)	P*
Age, y	72.4±9.0	70.5±9.9	0.04
Gender, M/F	138/66	127/83	0.15
Body weight, kg	82.7±17.7	86.7±20.6	0.03
Body mass index, kg/m <sup>2</sup>	29.2±5.3	30.2±5.8	0.06
Contrast volume, mL	133.7±74.4	136.4±71.6	0.70
Dose/body weight, g/kg	0.62±0.36	0.53±0.31	0.01
Diabetes mellitus, n (%)	78 (38.2)	92 (43.8)	0.27
Time of postdose sampling, n (%)			
45 to 71 hours	170 (83.3)	175 (83.3)	0.94
71 to 96 hours	27 (13.2)	29 (13.8)	
>96 hours	7 (3.5)	6 (2.9)	
Type of procedure, n (%)			
Dx cardioangiography	123 (60.3)	128 (61.0)	0.92
PCI	81 (39.7)	82 (39.0)	
NAC premedication, n (%)	79 (38.7)	89 (42.4)	0.48
Intravenous volume supplementation/body weight (mL/kg)	11.2±2.3	11.5±2.3	0.32
Predose eGFR (mL/min per 1.73 m <sup>2</sup> ), n (%)			
20 to 30	15 (7.4)	17 (8.1)	0.83
30 to 40	42 (20.6)	40 (19.1)	
40 to 50	82 (40.1)	78 (37.1)	
50 to 59	65 (31.9)	75 (35.7)	

Data are presented as mean±SD where appropriate.

\*t test for continuous variables; Fisher exact test for categorical variables.

### Incidence of CIN

Overall, the incidence of CIN by any definition was not statistically different in the 2 study groups (Table 3). The rate of absolute increases in SCr  $\geq 0.5$  mg/dL (44.2  $\mu$ mol/L), was 4.4% (9 of 204 patients) in the iopamidol-370 group and in 6.7% (14 of 210 patients) in the iodixanol-320 group (95% confidence interval [CI] of the difference,  $-6.7\%$  to  $2.1\%$ ;  $P=0.39$ ). A relative  $\geq 25\%$  increase in SCr was almost 2 times higher in both groups and occurred in 9.8% (20 of 204 patients) of the patients given iopamidol-370 and in 12.4% (26 of 210 patients) of the patients given iodixanol-320 (95% CI,  $-8.6\%$  to  $3.5\%$ ;  $P=0.44$ ). Decreases in eGFR  $\geq 25\%$  were recorded in 12 patients (5.9%) with iopamidol-370 and 21 patients (10.0%) with iodixanol-320 (95% CI,  $-9.3\%$  to  $1.1\%$ ;  $P=0.15$ ).

### Subgroup Analysis

The subgroup analysis of CIN occurrence by presence/absence of diabetes mellitus also showed no significant difference between the 2 agents, regardless of the CIN end point (Table 4). In 170 patients with CKD and diabetes mellitus, the rate of absolute increases in SCr  $\geq 0.5$  mg/dL (44.2  $\mu$ mol/L) was 5.1% (4 of 78 patients) with iopamidol-370 and 13.0% (12 of 92 patients) with iodixanol-320 (95% CI,  $-16.4\%$  to  $0.5\%$ ;  $P=0.11$ ). In 244 patients without diabetes, the primary outcome occurred at a rate of 4.0% (5 of 126 patients) with iopamidol-370 and 1.7% (2 of 118 patients) with iodixanol-320 (95% CI,  $-1.9\%$  to  $6.4\%$ ;  $P=0.45$ ).

Multivariate logistic regression analyses were performed with absolute ( $\geq 0.5$  mg/dL) or relative ( $\geq 25\%$ ) critical shifts

in SCr as dependent variables. Multivariate modeling that adjusted for risk factors confirmed that no differential CM effect existed (OR for iopamidol versus iodixanol, 0.66; 95% CI, 0.27 to 1.62;  $P=0.36$ ).

Clinically apparent worsening in renal status (oliguria, prolongation of hospitalization) was reported in only 2 patients (both were diabetics who received iodixanol-320). One of these patients received NAC prophylaxis. No patient required hemodialysis, and no study-related deaths were reported.

### Peak Changes in SCr and GFR

A significant difference in favor of iopamidol-370 was observed in mean postdose peak increases in SCr and peak decreases of eGFR from baseline in the study populations (Table 5). The mean peak increase in SCr for all patients ( $0.07\pm 0.22$  versus  $0.12\pm 0.23$  mg/dL,  $6.2\pm 19.5$  versus  $10.6\pm 20.3$   $\mu$ mol/L,  $P=0.03$ ) and for those with diabetes ( $0.07\pm 0.26$  versus  $0.16\pm 0.27$  mg/dL,  $6.2\pm 23.0$  versus  $14.1\pm 23.9$   $\mu$ mol/L,  $P=0.01$ ) was significantly less with iopamidol-370. The mean peak decrease in eGFR was also significantly less with iopamidol-370 for all patients ( $-2.2$  versus  $-4.0$ ,  $P=0.04$ ) and for diabetic patients ( $-2.1$  versus  $-5.0$ ,  $P=0.02$ ).

### Timing of Postdose Creatinine Determinations

Eighty-three percent of study patients had a postdose SCr measurement between 45 and 71 hours. No difference in the incidence of CIN was seen between the agents in these

**TABLE 2. Baseline Biochemical Characteristics of Study Patients**

Group and Characteristic	Iopamidol-370 Group	Iodixanol-320 Group	<i>P</i> *
Total population, n	204	210	
Predose SCr, mg/dL	1.46±0.36	1.44±0.41	0.64
Predose eGFR, mL/min per 1.73 m <sup>2</sup>	49.3±11.6	50.2±13.0	0.45
Patients without diabetes mellitus	n=126	n=118	
Predose SCr, mg/dL	1.40±0.30	1.34±0.33	0.14
Predose eGFR, mL/min per 1.73 m <sup>2</sup>	50.7±10.9	52.3±12.3	0.28
Patients with diabetes mellitus, n	78	92	
Predose SCr, mg/dL	1.56±0.43	1.57±0.47	0.80
Predose eGFR, mL/min per 1.73 m <sup>2</sup>	47.1±12.4	47.5±13.4	0.81
No pretreatment with NAC, n	125	121	
Predose SCr, mg/dL	1.47±0.36	1.47±0.38	0.94
Predose eGFR, mL/min per 1.73m <sup>2</sup>	49.8±11.8	49.5±12.9	0.85
Pretreatment with NAC, n	79	89	
Predose SCr, mg/dL	1.45±0.36	1.42±0.45	0.57
Predose eGFR, mL/min per 1.73 m <sup>2</sup>	48.6±11.4	51.3±13.2	0.16
Diagnostic cardioangiography, n	123	128	
Predose SCr, mg/dL	1.46±0.37	1.44±0.43	0.70
Predose eGFR, mL/min per 1.73 m <sup>2</sup>	49.2±11.5	49.9±13.2	0.65
PCI, n	81	82	
Predose SCr, mg/dL	1.47±0.34	1.46±0.39	0.81
Predose eGFR, mL/min per 1.73 m <sup>2</sup>	49.6±11.8	50.8±12.8	0.52

Data are presented as mean±SD where appropriate.

\**t* test.

patients. Overall, the timing of the postdose serum creatinine did not alter the absence of a difference in CIN incidence between the contrast agents (Table 6).

### Nonrenal Adverse Events

Most of the adverse events in the study were nonserious and self-resolving with both agents. No serious cardiac adverse events (emergency recatheterization for documented signs of ischemia, Q wave or non-Q wave acute myocardial infarction, pulmonary edema, etc.) were observed throughout the study. One patient developed an ischemic stroke 50 minutes after administration of iodixanol-320. The event was considered to be unrelated to the study agent by the investigator.

## Discussion

### Main Findings

The major finding of this study is that, among a population of high-risk patients who underwent cardiac catheterization procedures, no significant difference existed in the occurrence of CIN between the low-osmolality, nonionic monomer

iopamidol-370 (796 mOsm/kg) and the iso-osmolality dimer iodixanol-320 (290 mOsm/kg). The CIs for the primary outcome (Table 3) also indicate that if the trial were to be repeated many times, the “true” rate of CIN would fall within 95% of the calculated CIs, −6.7% to 2.1% (this favors iopamidol). These differences are not likely to be clinically significant. Although trends in favor of iopamidol were also seen in the subset of patients with diabetes mellitus, none of the observed differences were statistically significant.

### Prior Studies

The most recent prospective randomized trial, the RECOVER study,<sup>12</sup> also showed that the rate of CIN after the nonionic dimer iodixanol was not significantly different from that seen with the low-osmolality ionic dimer ioxaglate when the absolute ( $\geq 0.5$  mg/dL) or the relative ( $\geq 25\%$ ) increase in SCr end points were assessed separately in the study population. However, when both end points were assessed together, 7.9% of patients in the iodixanol group and 17% of patients in the ioxaglate group had an increase in SCr from

**TABLE 3. Incidence of CIN, Total Population**

Postdose	Iopamidol-370 Group (n=204)	Iodixanol-320 Group (n=210)	Absolute Difference (95% CI)	<i>P</i> *
Increase of $>0.5$ mg/dL in SCr, n (%)	9 (4.4)	14 (6.7)	−2.3 (−6.7, 2.1)	0.39
Increase of $>25\%$ in SCr, n (%)	20 (9.8)	26 (12.4)	−2.6 (−8.6, 3.5)	0.44
Decrease of $>25\%$ in eGFR, n (%)	12 (5.9)	21 (10)	−4.1 (−9.3, 1.1)	0.15

\*Fisher exact test.

**TABLE 4. Incidence of CIN: Subgroups of Patients Without and With Diabetes Mellitus**

Subgroups and Postdose	Iopamidol-370 Group		Iodixanol-320 Group		Absolute Difference (95% CI)	P*
	N	n (%)	N	n (%)		
Patients without diabetes mellitus						
Increase of >0.5 mg/dL in SCr	126	5 (4.0)	118	2 (1.7)	2.3 (−1.9 to 6.4)	0.45
Increase of >25% in SCr	126	12 (9.5)	118	12 (10.2)	−0.7 (−8.1 to 6.8)	1.00
Decrease of >25% in eGFR	126	7 (5.6)	118	9 (7.6)	−2.0 (−8.3 to 4.2)	0.61
Patients with diabetes mellitus						
Increase of >0.5 mg/dL in SCr	78	4 (5.1)	92	12 (13.0)	−7.9 (−16.4 to 0.5)	0.11
Increase of >25% in SCr	78	8 (10.3)	92	14 (15.2)	−4.9 (−14.9 to 5.0)	0.37
Decrease of >25% in eGFR	78	5 (6.4)	92	12 (13.0)	−6.6 (−15.4 to 2.1)	0.20

\*Fisher exact test.

baseline of  $\geq 25\%$  and/or  $\geq 0.5$  mg/dL within 2 days of CM administration ( $P=0.021$ ). With that composite CIN end point, the occurrence of CIN was also higher after the ionic CM in the subsets of patients with diabetes and/or creatinine clearance  $<30$  mL/min. The RECOVER authors conclude with the suggestion that their results support the hypothesis that CM osmolality, rather than viscosity or ionicity, is an important factor in CIN. However, in the CARE study, when both SCr end points were assessed together, the rate of CIN was similar after the administration of the isotonic iodixanol (10.3% with iopamidol-370 versus 12.9% with iodixanol-320; 95% CI,  $-8.7\%$  to  $3.6\%$ ;  $P=0.45$ ).

In the NEPHRIC study by Aspelin et al,<sup>8</sup> the primary end point for CIN was the mean peak increase in SCr after CM administration. In that study, mean peak SCr increases were significantly lower in patients given iodixanol-320 ( $0.13 \pm 0.22$  mg/dL,  $11.5 \pm 19.5$   $\mu$ mol/L) compared with those given iohexol-350 ( $0.55 \pm 0.98$  mg/dL,  $48.6 \pm 86.6$   $\mu$ mol/L,  $P=0.001$ ).<sup>8</sup> In the CARE study, although mean peak increases in SCr after iodixanol-320 in patients with CKD and diabetes were similar to those observed in the NEPHRIC study ( $0.16 \pm 0.27$  mg/dL,  $14.1 \pm 23.9$   $\mu$ mol/L), mean changes after iopamidol-370 ( $0.07 \pm 0.26$  mg/dL,  $6.2 \pm 23.0$   $\mu$ mol/L) were markedly less than those reported for iohexol-350. In fact, in the CARE study the mean postdose elevation of SCr

levels, both for all patients and for the subgroup of diabetics, was significantly lower with iopamidol-370 than with iodixanol-320.

The findings of the CARE study are also interesting in light of a recently published meta-analysis of double-blind, randomized, controlled trials, which compared iodixanol with several other low-osmolality CM in adult patients who underwent angiographic examinations.<sup>15</sup> In that meta-analysis, the maximum SCr increase within 3 days after CM administration in patients with CKD was significantly smaller in the iodixanol group compared with the pooled group of other low-osmolality CM (0.07 mg/dL versus 0.16 mg/dL,  $6.2$   $\mu$ mol/L versus  $14.1$   $\mu$ mol/L,  $P=0.004$ ) as well as in the subgroup of CKD patients with diabetes (0.10 mg/dL versus 0.33 mg/dL,  $8.8$   $\mu$ mol/L versus  $29.2$   $\mu$ mol/L,  $P=0.003$ ). However, the timing of postdose sampling varied across the studies included in that meta-analysis, and different labs were used in the various studies. Moreover, the distribution of patients given the various low-osmolality CM was unbalanced, as most of the patients in the low-osmolality CM groups received the nonionic monomer iohexol ( $n=381$ , 28.3%) or the ionic dimer ioxaglate ( $n=789$ , 58.7%), and only a small proportion of patients received iopamidol ( $n=69$ , 5.1%) or iopromide ( $n=06$ , 7.9%). In fact, the 1 study that compared iodixanol and iopamidol in that meta-analysis showed a favorable trend with iopamidol.<sup>16</sup>

**TABLE 5. Changes From Baseline for SCr and eGFR**

	Iopamidol-370 Group		Iodixanol-320 Group		P*
	N	Mean Change $\pm$ SD	N	Mean Change $\pm$ SD	
Total population					
SCr, mg/dL	204	$0.07 \pm 0.22$	210	$0.12 \pm 0.23$	0.032
eGFR, mL/min per 1.73 m <sup>2</sup>	204	$-2.16 \pm 7.86$	210	$-4.02 \pm 8.10$	0.038
Patients without diabetes mellitus					
SCr, mg/dL	126	$0.07 \pm 0.19$	118	$0.08 \pm 0.18$	0.708
eGFR, mL/min per 1.73 m <sup>2</sup>	126	$-2.23 \pm 7.18$	118	$-3.28 \pm 8.35$	0.695
Patients with diabetes mellitus					
SCr, mg/dL	78	$0.07 \pm 0.26$	92	$0.16 \pm 0.27$	0.013
eGFR, mL/min per 1.73 m <sup>2</sup>	78	$-2.05 \pm 8.90$	92	$-4.97 \pm 7.65$	0.016

\*P value for comparison of contrast agent groups based on ANCOVA model.

TABLE 6. Incidence of CIN by Postdose Sampling Time Point

Postdose time ranges in hours, n/N (%)	Increase of >0.5 mg/dL in SCr		Increase of >25% in SCr		Decrease of >25% in eGFR	
	Iopamidol-370	Iodixanol-320	Iopamidol-370	Iodixanol-320	Iopamidol-370	Iodixanol-320
45 to 71	5/170 (2.9)	13/175 (7.4)	11/170 (6.5)	22/175 (12.6)	6/170 (3.5)	17/175 (9.7)
71 to 96	4/27 (14.8)	1/29 (3.4)	8/27 (29.6)	4/29 (13.8)	5/27 (18.5)	4/29 (13.8)
>96	0/7	0/6	1/7 (14.3)	0/6	1/7 (14.3)	0/6
<i>P</i> *	0.328		0.417		0.125	

\*CMH test to test overall treatment effect.

The CARE study included 170 patients with both CKD and diabetes. A trend toward lower CIN rates was observed after iopamidol-370 in this high-risk subgroup, whereas in a previous study of 129 diabetics with CKD (the NEPHRIC study<sup>8</sup>) the occurrence of CIN after iodixanol-320 was markedly and significantly lower than after the low-osmolality iohexol-350 (844 mOsm/kg). The results of the CARE study, as well as those of the NEPHRIC study, correspond well with the findings of systematic reviews of CIN trials<sup>17,18</sup> and the findings of a recent analysis of renal adverse events in the Food and Drug Administration postmarketing safety databases.<sup>18</sup> This emerging body of evidence, now reinforced by the results of the present trial, shows that when iodixanol is used as common comparator agent, iohexol has a greater incidence of CIN and iopamidol has a lower incidence of CIN. Although study design and patient characteristics differ in minor ways between these studies, the inescapable conclusion is that iohexol and iopamidol, both low-osmolality CMs, have different renal safety profiles. This conclusion, together with the observations in the present trial of a similar renal safety profile of the low-osmolality iopamidol compared with iso-osmolality iodixanol, argues against the concept that osmolality is the primary determinant of renal toxicity, at least for low-osmolality CM.

### Strengths and Limitations

The present study is the largest, prospective, randomized, double-blind comparison of the iso-osmolality iodixanol-320 with a low-osmolality CM in high risk patients, including a sizable cohort of patients with CKD and diabetes mellitus. The study was designed to detect differences in absolute rates of CIN between 8.5% and 11.9% depending on the absolute incidence of CIN in the lowest CIN group. We anticipated an overall incidence of CIN to be  $\approx 15\%$ . We observed a lower incidence of CIN, perhaps as a result of the nature of the prophylactic therapy (bicarbonate in all patients and NAC in most patients),<sup>19</sup> the use of a primary definition of CIN that underestimates renal injury in patients with a baseline creatinine <2.0 mg/dL,<sup>20</sup> or because the 2 agents chosen are among those with the lowest rates of nephrotoxicity.<sup>17</sup> It would have taken  $\approx 3300$  patients for the 2.3% absolute difference in CIN rate that favored iopamidol (CIN definition,  $\geq 0.5$  mg/dL creatinine increase) to reach statistical significance. Thus the study sample is of sufficient size to reassure us that possible 'true' differences between these 2 agents are very small and not likely to be of clinical significance.

The distribution of patients in the 2 study groups by presence or absence of diabetes and the degree of renal

impairment was well balanced. Renal impairment was defined by an eGFR <60 mL/min per 1.73 m<sup>2</sup> by the abbreviated MDRD formula. This formula is considered more accurate than the Cockcroft-Gault formula in patients with renal insufficiency, has been validated in patients with a variety of comorbidities, and is recommended by the National Kidney Foundation.<sup>3</sup> Had we used the Cockcroft-Gault formula for enrollment purposes, some patients would have been excluded because of an estimated creatinine clearance >60 mL/min. However, we repeated the analyses without these patients and found no differences in the outcome of CIN between the 2 contrast agents. For the first time in a CIN study, exact timing of postdose blood sampling for SCr was reported and was comparable in the 2 study groups.

However, despite randomization, some significant differences existed in the characteristics of the evaluable patients who received the 2 study agents. The iopamidol-370 group was overall at higher risk, with a significantly older patient population, significantly more patients in the  $\geq 65$  year age group, and a significantly larger mean iodine dose. However, these differences between the study groups were unlikely to be large enough to be relevant to the absence of difference in CIN between the 2 groups, despite the observed trend in favor of a reduced incidence of CIN with iopamidol-370. Besides, multivariate logistic regression analysis with the primary CIN end point of  $\geq 0.5$  mg/dL increase in SCr was performed, and only 2 risk factors were identified: diabetes mellitus (OR, 3.2; 95% CI, 1.2 to 8.6;  $P=0.025$ ) and baseline levels of SCr (OR, 3.8; 95% CI, 1.4 to 10.8;  $P=0.011$ ), but not either age or contrast dose.

The incidence of renal complications was very low in the CARE study (2 cases, both in the iodixanol-320 group, did not require hemodialysis and recovered without sequelae), so that no conclusions can be drawn about the propensity of the 2 agents to cause more serious acute renal failure.

Finally, the CARE study was not designed to collect outcome data on longer-term consequences of exposure to iopamidol-370 versus iodixanol-320. A recent retrospective comparison of iodixanol-320 with iobitridol-350 (915 mOsm/kg) in CKD patients who underwent cardiac or peripheral angiography showed that the incidence of CIN, as well as the incidence of major adverse events at 1-year follow-up (death, myocardial infarction, end-stage renal failure that required dialysis, percutaneous revascularization), was similar with the 2 CM.<sup>9</sup> Because in the CARE study no differences in CIN occurrence were observed, it is reasonable to expect no



significant differences in long-term morbidity and mortality from exposure to iopamidol-370 or iodixanol-320.

### Conclusions

The rate of CIN in high-risk patients who undergo cardiac angiography or percutaneous coronary intervention is not statistically different between use of iopamidol-370 or iodixanol-320. Iopamidol-370 demonstrated a significantly smaller mean increase of SCr. Therefore, iopamidol-370 may be used at least as safely as iodixanol-320 in this high-risk clinical setting.

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### Disclosures

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### References

- Thom T, Haases N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC Jr, Hong Y, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wassertheil-Smolter S, Wilson M, Wolf P. Heart disease and stroke statistics - 2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006;113:e85-e151.
- Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis*. 2002;39:930-936.
- National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39:S1-S266.
- Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney Int*. 2006;69:S11-S15.
- Parfrey P, Griffiths SM, Barrett BJ, Paul MD, Genge M, Withers J, Farid N, McManamon PJ. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. *N Engl J Med*. 1989;320:143-149.
- Nikolsky E, Mehran R, Turcot D, Aymong ED, Mintz GS, Lasic Z, Lansky AJ, Tsounias E, Moses JW, Stone GW, Dangas GD. Impact of chronic kidney disease on prognosis of patients with diabetes mellitus treated with percutaneous coronary intervention. *Am J Cardiol*. 2004;94:300-305.
- Lautin E, Freeman NJ, Schoenfeld AH, Bakal CW, Haramati N, Friedman AC, Lautin JL, Braha S, Kadish ED, Sprayregen S. Radiocontrast-associated renal dysfunction: incidence and risk factors. *Am J Roentgenol*. 1991;157:49-58.
- Aspelin P, Aubry P, Fransson S, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med*. 2003;348:491-499.
- Briguori C, Colombo A, Airolidi F, Morici N, Sangiorgi GM, Violante A, Focaccio A, Montorfano M, Carlino M, Condorelli G, Ricciardelli B. Nephrotoxicity of low-osmolality versus iso-osmolality contrast agents: impact of N-acetylcysteine. *Kidney Int*. 2005;68:2250-2255.
- Chalmers N, Jackson RW. Comparison of iodixanol and iohexol in renal impairment. *Br J Radiol*. 1999;72:701-703.
- Carraro M, Malalan F, Antonione R, Stacul F, Cova M, Petz S, Assante M, Grynne B, Haider T, Palma LD, Faccini L. 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.
- Jo S, Youn TJ, Koo BW, Park JS, Kang HJ, Cho YS, Chung WY, Joo GW, Chae IH, Choi DJ, Oh BH, Lee MM, Park YB, Kim HS. Renal toxicity evaluation and comparison between Visipaque (Iodixanol) and Hexabrix (Ioxaglate) in patients with renal insufficiency undergoing coronary angiography: the RECOVER study: a randomized controlled trial. *J Am Coll Cardiol*. 2006;48:924-930.
- Johnson C, Levey AS, Coresh J, Levin A, Lau J, Eknoyan G. Clinical practice guidelines for chronic kidney disease in adults: part II: glomerular filtration rate, proteinuria, and other markers. *Am Fam Physician*. 2004;70:1091-1097.
- 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.
- McCullough P, Bertrand ME, Brinker JA, Stacul F. A meta-analysis of the renal safety of isosmolar iodixanol compared with low-osmolar contrast media. *J Am Coll Cardiol*. 2006;48:692-699.
- Verow P, Nossen JO, Sheppick A, Kjaersgaard P. A comparison of iodixanol with iopamidol in aorto-femoral angiography. *Br J Radiol*. 1995;68:973-978.
- 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.
- 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.
- Briguori C, Airolidi F, D'Andrea D, Bonizzoni E, Morici N, Focaccio A, Michev I, Montorfano M, Carlino M, Cosgrave J, Ricciardelli B, Colombo A. Renal insufficiency following contrast media administration trial (REMEDIAL). A randomized comparison of 3 preventive strategies. *Circulation*. 2007;115:1211-1217.
- Solomon R, Barrett B. Follow-up of patients with contrast-induced nephropathy. *Kidney Int*. 2006;69:S46-S50.

### CLINICAL PERSPECTIVE

The Cardiac Angiography in Renally Impaired Patients (CARE) study was a multicenter, double-blind, randomized study designed to prospectively compare the incidence of contrast-induced nephropathy (CIN) after intraarterial administration of the low-osmolality iopamidol-370 (796 mOsm/kg; n=204 patients) or the iso-osmolality iodixanol-320 (290 mOsm/kg; n=210 patients) in 414 patients with moderate to severe chronic kidney disease (glomerular filtration rate, 20 to 59 mL/min per 1.73 m<sup>2</sup>) who underwent cardiac angiography or percutaneous coronary interventions. All patients received intravenous bicarbonate prophylaxis, and some patients also received N-acetylcysteine. The primary CIN end point was a postdose serum creatinine increase  $\geq 0.5$  mg/dL (44.2  $\mu$ mol/L) over baseline. Secondary CIN end points were a postdose serum creatinine increase  $\geq 25\%$ , a postdose glomerular filtration rate decrease of  $\geq 25\%$ , and the mean peak change in serum creatinine. Independent of the CIN end point used, no significant difference existed between the contrast agents in the occurrence of CIN between the 2 contrast media overall and in the subgroup of chronic kidney disease patients with diabetes mellitus. Iopamidol-370 caused significantly smaller mean peak increases in serum creatinine. In conclusion, iopamidol-370 may be used at least as safely as iodixanol-320 in high-risk patients who must undergo cardiac catheterization procedures.