The ACTIVE Trial: Comparison of the Effects on Renal Function of Iomeprol-400 and Iodixanol-320 in Patients With Chronic Kidney Disease Undergoing Abdominal Computed Tomography

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Background: We performed a multicenter, double-blind, randomized, parallel-group study to compare the renal effects of iomeprol-400 and iodixanol-320 in patients with preexisting chronic kidney disease undergoing contrast-enhanced multidetector computed tomography of the liver.

Methods: One hundred forty-eight patients with moderate-to-severe chronic kidney disease, ie, serum creatinine (SCr) ≥1.5 mg/dL (132.6 μmol/L) and/or calculated creatinine clearance (CrCl) <60 mL/min, undergoing contrast-enhanced multidetector computed tomography of the liver were randomized to equi-iodine doses (40 gI) of either the low-osmolar agent iomeprol-400 (400 mgI/mL, 726 mOsm/kg, N = 76) or the isotonic agent iodixanol-320 (320 mgI/mL, 290 mOsm/kg, N = 72), injected intravenously at 4 mL/S, followed by a bolus of 20 mL normal saline solution at the same rate. SCr was obtained at screening, baseline and at 48 to 72 hours postdose. SCr measurements and CrCl calculations were performed by a central laboratory. Contrast-induced nephropathy (CIN) was defined as an absolute SCr increase of ≥0.5 mg/dL (44.2 μmol/L) from baseline to 48 to 72 hours postdose. Mean SCr changes from baseline were also assessed. A Renal Safety Review Board comprised 3 medical experts reviewed the renal safety data, demographics, medical history, CIN risk factors, concomitant medications, and hydration status of each subject in a blinded manner.

Results: The 2 study groups were comparable with regard to age, gender distribution, concomitant nephrotoxins, hydration status, and total iodine dose; however, the iomeprol-400 group showed a significantly higher proportion of patients with diabetes mellitus ($P = 0.02$). Baseline SCr was 1.7 ± 0.6 mg/dL (150.3 ± 53.0 μmol/L) in the iomeprol-400 group and 1.7 ± 0.7 mg/dL (150.3 ± 61.9 μmol/L) in the iodixanol-320 group ($P = 0.87$). Predose CrCl was 41.5 ± 13.1 mL/Min in the iomeprol-400 group and 43.0 ± 13.3 mL/Min in the iodixanol-320 group ($P = 0.49$). Five of 72 patient receiving iodixanol-320 (6.9%) and none of the patients receiving iomeprol-400 showed an increase of ≥0.5 mg/dL (44.2 μmol/L) from baseline [$P = 0.025$, 95% CI (−12.8%, −1.1%)]. The mean SCr change from baseline was significantly higher ($P = 0.017$ ANCOVA) after iodixanol-320 (0.06 ± 0.27) than after iomeprol-400 (−0.04 ± 0.19).

Conclusions: The incidence of CIN was significantly higher after IV administration of iodixanol-320 than iomeprol-400. The mean rise in SCr from baseline was also higher in patients receiving iodixanol.

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

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Following the introduction of multidetector computed tomography (MDCT) technology, the number of patients undergoing contrast-enhanced CT studies has steadily grown in the past 6 years. In 2006, it was on the order of >20 million studies in the European Union, and >31 million in the United States.[1] Although the benefits of contrast-enhanced MDCT are well known in diagnosing diseases and trauma and in the guidance of interventional and therapeutic procedures, those benefits are not without risks. Postcontrast adverse events, associated with the use of an iodinated contrast medium (CM), remain a source of concern. Most adverse events occur within the first 60 minutes following the CM administration, with the greatest risk in the first 10 minutes.[2] More delayed CM adverse events do occur, with

some events recorded up to 7 days after contrast injection. Contrast-induced nephropathy (CIN) is a well-known serious complication of CM use. CIN is defined as an acute deterioration of renal function after the administration of iodinated contrast media in the absence of other causes.[2,3] In clinical studies, it is detected as an increase of 25% or more, or as an absolute increase of 0.5 mg/dL (44.2 μmol/L) or more in serum creatinine (SCr) from baseline value.[2,3] Moderate-to-severe chronic kidney disease (CKD), defined as glomerular filtration rate stably below 60 mL/Min/1.73 m^2, is the most important factor for the development of CIN.[2,3] In approximately 80% of CIN cases, SCr starts to increase within the first 24 hours after the exposure to iodinated CM.[4] The peak SCr increase usually occurs within 48 to 72 hours post-CM, with a return to baseline or near baseline within 7 to 10 days in most cases.[2,3]

The majority of the CIN studies have evaluated the nephrotoxicity of the intra-arterial administration of iodinated CM in patients with renal failure undergoing cardiac angiography and intervention.[5,6] After intra-arterial administration of contrast, critical increases in SCr, even if transient, have been associated with a long-term increase in cardiovascular events, worsening of renal failure and mortality.[7–13] However, no association between CIN after intravenous (IV) contrast and long-term morbidity and mortality has ever been reported. Data on the incidence of CIN after IV CM administration are limited, and even fewer data are available to understand whether there are any significant differences in nephrotoxic potential among the various iodinated CM after their IV use in high-risk patients.[5,6]

The Abdominal Computed Tomography: Iomeron® 400 versus Visipaque™ 320 Enhancement (ACTIVE) study was a prospective, multicenter study performed to compare the effects on renal function and incidence of CIN after the intravenous injection of equi-iodine doses of iomeprol-400 (Iomeron 400, Bracco Imaging, Milan, Italy; 400 mgI/mL, 726 mOsm per kg of water) and iodixanol-320 (Visipaque 320, GE Healthcare, Chalfont St. Giles, United Kingdom; 320 mgI/mL, 290 mOsm per kg of water) in patients with moderate-to-severe CKD undergoing MDCT imaging of the liver.

MATERIALS AND METHODS

Study Design

The ACTIVE trial was a prospective, multicenter, double-blind, randomized, parallel group comparison of iomeprol-400 and iodixanol-320 in renally impaired patients receiving relatively high doses (40 g of iodine, gI) of IV contrast. The study was conducted according to Good Clinical Practice standards at 12 centers in Europe and at 4 centers in the People's Republic of China (see Appendix). The study was performed in accordance with the Declaration of Helsinki (Helsinki, Finland, 1964) and all subsequent amendments. Each participating center's Ethics Committee or Institutional Review Board approved the protocol, and all study patients provided written informed consent at the time of their enrollment into the study.

Study Patients

Patients aged 18 years or older with baseline SCr stably ≥1.5 mg/dL (≥133 μmol/L) and/or creatinine clearance (CrCl) between 10 and 59 mL/Min/1.73 m^2, referred for a clinically indicated contrast-enhanced MDCT examination of the liver, were enrolled in a consecutive manner at each study center. The stability of renal function levels was assessed by comparing CrCl values obtained within 6 months and within 2 weeks of the CT examination. CKD was considered stable if the average daily variation between precontrast screening CrCl values was ≤3%. Patients were excluded from the study if they did not fulfill the inclusion criteria, or if they had a history of hypersensitivity to iodine-containing compounds, suspicion of hyperthyroidism or thyroid malignancies, unstable renal function, acute renal failure requiring dialysis, severe congestive heart failure (NYHA class III–IV), uncontrolled diabetes, or if they were pregnant or lactating females. Patients were also excluded if they had undergone or were scheduled to undergo any other radiologic procedure utilizing x-ray contrast media from 72 hours before to 7 days after the administration of the study agent, if they received an investigational compound within 30 days before admission to the study, or if they had any medical condition or other circumstances that would have significantly decreased the chances of obtaining reliable data or achieving postdose follow-up examinations.

Study Protocol

Once enrolled, patients were randomized to receive 40 gI as either iomeprol-400 or iodixanol-320 for their CT procedure. A third party drug dispensing professional at each site managed the preparation, dispensing, and accountability of all trial contrast media, as per code assignment. The drug dispensing professional did not participate in any of the study assessments, and all other individuals associated with the study remained blinded until the database was locked and the data analyzed. The contrast agents were warmed to body temperature (37°C) and administered intravenously at a rate of 4 mL/S using a mechanical power injector. All contrast media injections were followed by a 20-mL bolus of normal saline administered at the same rate. Injections were made through an angio catheter, placed in an antecubital vein (preferable), or in a peripheral vein of the upper arm or forearm (alternative). Volume supplementation was left to the discretion of the investigators, as per their local hydration protocols. No preventative drug treatments (eg, fenoldopam, acetylcysteine, theophylline) were to be administered to study patients. If administered, type, time, and dosage of the prophylactic treatment used was recorded and reported. The investigators also noted the administration of any potentially nephrotoxic medications. These included chronically administered nonsteroidal anti-inflammatory drugs, immunosuppressive agents such as cyclosporine, aminoglycosides such as gentamycin, and certain chemotherapeutic agents such as cisplatin.

Collection and Analysis of Baseline and Postdose SCr Data

SCr measurements were obtained within 72 hours before CM administration, and at 48 to 72 hours after CM administration. Evaluations for SCr and calculated CrCl were performed by central laboratories (Covance Central Labora-

tory Services, Geneva, Switzerland, for the European centers, MDS Pharma Services Central Laboratory China, for centers in China). A Roche Modular Analyzer and the same commercial reagents were used for all SCr determinations. The assay used was a substrate triggered, rate-blanked method, utilizing a modification of the Jaffe reaction. CrCl was calculated using the Cockcroft–Gault formula.[14] CIN was defined as an absolute increase in SCr from baseline of ≥0.5 mg/dL (44.2 μmol/L) at 48 to 72 hours after contrast media administration. Postdose increases in SCr of ≥25% or decreases in CrCl of ≥25% were also assessed, as was the mean postdose SCr change from baseline. Each subject was evaluated for the incidence of CIN at 48 to 72 hours postdose. If a subject showed an increase of ≥0.5 mg/dL SCr (44.2 μmol/L) from baseline at 48 to 72 hours postdose, a follow-up SCr measurement was to be obtained on day 7. Any changes in concomitant medications, and general observations of the subject's clinical renal status, including any notation of the onset of renal dialysis, or death, were also noted.

CIN Endpoints

The primary CIN endpoint of the study was an increase in SCr ≥0.5 mg/dL (44.2 μmol/L) at 48 to 72 hours after CM administration. Relative rises in SCr ≥25%, decreases in CrCl ≥25% from baseline and mean SCr changes from baseline were secondary endpoints of the study.

Data Analysis

Before the unblinding of the study data, a Renal Safety Review Board consisting of 3 medical experts on contrast media safety (H.S.T, S.K.M, C.M.E.) reviewed the pre- and postdose renal safety data, and other necessary related data (eg, demographics, medical history, risk factors for CIN, concomitant medications, timing of blood withdrawals) of each subject to determine whether the requirements of the protocol had been met and the subject was suitable for inclusion in the CIN analysis. Statistical testing was performed based on 2-sided tests at the 0.05 level of significance with 95% confidence limits. Summary statistics (mean and SD) were generated for continuous variables (age, body weight, body mass index, contrast dose, dose of contrast by body weight, volume of IV hydration, SCr, CrCl). The number and percentage of patients in each category were provided for categorical data (gender, race, presence or absence of diabetes mellitus, use of any volume supplementation, and concomitant nephrotoxic medications). Demographics and baseline patient characteristics data were summarized by contrast agent group. A χ^2 test was used to test for differences between the iopamidol and iodixanol populations in categorical variables at baseline, whereas the unpaired *t* test was used to test for differences in continuous variables. After confirmation of normal distribution, predose SCr and CrCl were also compared across the groups before contrast by unpaired *t* test. Postcontrast changes in SCr were summarized as mean and 1 SD. Mean changes from baseline in SCr and CrCl were also tested for normality and evaluated with analysis of covariance (ANCOVA), using the predose SCr measurement as covariate. The rates of increases in SCr ≥0.5 mg/dL or 25% and decreases in CrCl ≥25% from baseline were analyzed using Fisher exact test. An analysis of CIN rates was also performed in the subset of patients with baseline CrCl ≤40 mL/Min and/or SCr ≥2.0 mg/dL. Logistic regression analyses were performed, using CIN as the dependent variable, contrast agents as treatment groups, and risk factors such as age, gender, diabetes mellitus, volume supplementation, predose SCr, total dose by body weight, and concomitant use of nephrotoxic medications as covariates. Statistical tables and analyses were generated using SAS® Version 8.2 (SAS Institute, Cary, NC) under Windows operating system.

RESULTS

A total of 184 patients were enrolled in the study between July 2005 and October 2006, of whom 92 were randomized to receive iomeprol-400 and 92 iodixanol-320. A mean of 11.5 patients were enrolled per site (range, 1–40). Of the 184 patients randomized, 183 were given contrast (91 iomeprol-400 and 92 iodixanol-320), whereas one patient withdrew his consent before the CT examination. The CIN analysis population consisted of 148 patients, of whom 76 received iomeprol-400 and 72 iodixanol-320. Before the data were unblinded, 35 patients (15 in the iomeprol group and 20 in the iodixanol group) were excluded from the CIN analysis by the Renal Safety Review Board for one or more of the following reasons: screening CrCl >59 mL/min (3 patients); lack of a screening SCr value (n = 5); unstable renal function (17 patients); sample for SCr drawn <45 hour postcontrast (2 patients) or >78 hours postcontrast (1 patient); or no predose and/or postdose SCr values (11 patients). The disposition of patients enrolled in the study is further detailed in Figure 1. All patients excluded from the CIN analysis received the same iodine dose (40 gI) as the remainder of the enrolled population, and none experienced CIN by any metric used.

The 2 study groups were comparable with regard to age, gender distribution, concomitant nephrotoxic medications, hydration status, and total iodine dose. However, the iomeprol-400 group had a significantly higher proportion of patients with diabetes mellitus ($P = 0.02$, Table 1). A total of 13.2% and 11.1% of the patients were hydrated in the iomeprol-400 and iodixanol-320 groups, with volumes of hydration ranging from 1125.0 mL (16.2 mL/kg) in the iomeprol group to 1368.8 mL (17.6 mL/kg) in the iodixanol group. Baseline SCr was 1.7 ± 0.6 mg/dL (149.4 ± 53.0 μmol/L) in the iomeprol-400 group and 1.7 ± 0.7 mg/dL (151.2 ± 64.5 μmol/L) in the iodixanol-320 group ($P = 0.87$). Predose CrCl was 41.5 ± 13.1 mL/Min/1.73 m^2 in the iomeprol group and 43.0 ± 13.3 mL/Min/1.73 m^2 in the iodixanol group ($P = 0.49$).

Contrast-Induced Nephropathy

The incidence of CIN in the 2 study groups is presented in Tables 2 and 3. An absolute increase of ≥0.5 mg/dL (44.2 μmol/L) in SCr was observed in 5 of the 72 (6.9%) patients who received iodixanol-320 and in none of the patients who received iomeprol-400 [95% CI (−12.8%, −1.1%), $P = 0.025$]. Relative rises in SCr of ≥25% and relative CrCl decreases of ≥25% SCr occurred with similar frequency in both groups ($P > 0.05$, Table 2).

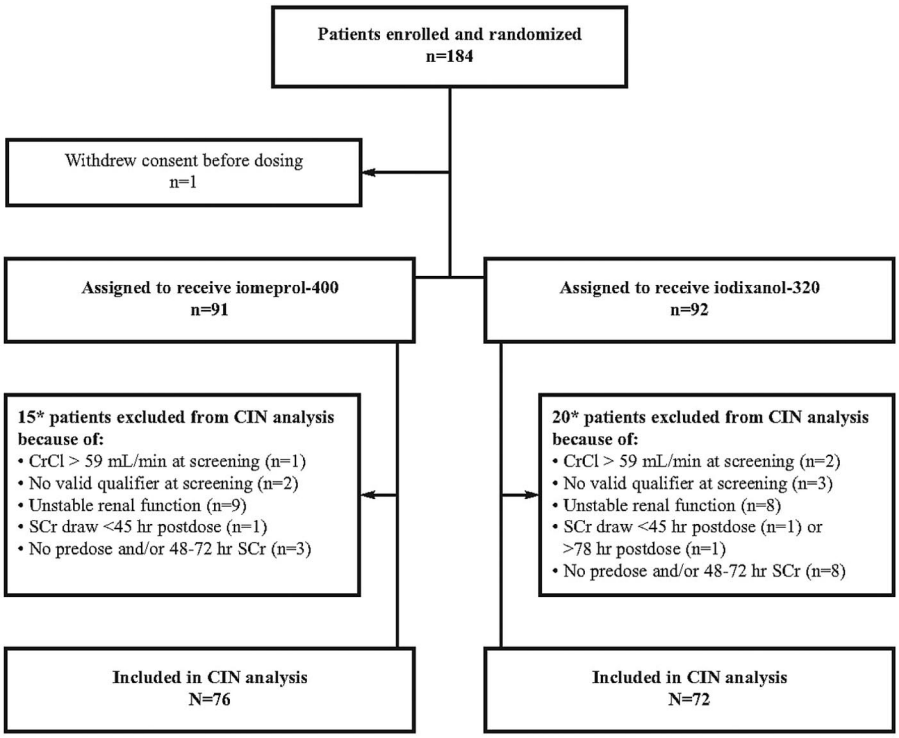

FIGURE 1. Flow of patients through the study.

TABLE 1. Baseline and Procedural Characteristics of Study Patients

Characteristic	Iomeprol-400 (N = 76)	Iodixanol-320 (N = 72)	*P**
Mean age (yrs)	67.1 ± 14.1	65.4 ± 12.1	0.42
Gender (M/F)	58/18	46/26	0.10
Body weight (kg)	66.7 ± 12.6	67.9 ± 13.2	0.55
Body mass index (kg/m^2)	24.2 ± 4.0	24.7 ± 3.9	0.42
Diabetes mellitus N (%)	21 (27.6)	9 (12.5)	0.02
Concomitant nephrotoxic medications	7 (9.2)	10 (13.9)	0.37
Baseline serum creatinine (mg/dL)**	1.7 ± 0.6	1.7 ± 0.7	0.87
Baseline creatinine clearance (mL/Min)	41.5 ± 13.1	43.0 ± 13.3	0.49
Hydration performed N (%)	10 (13.2)	8 (11.1)	0.70
Volume of intravenous hydration (mL)	1125 ± 358	1369 ± 1070	0.55
Total dose of contrast (gI)	40.0 ± 0.0	40.0 ± 0.0	1.0
Dose (gI)/body weight (kg)	0.6 ± 0.1	0.6 ± 0.1	0.62

*A χ^2 test was used to test for differences in categorical variables between the iopamidol and iodixanol study groups, whereas differences in continuous variables were tested with an unpaired *t* test.

**To convert values for serum creatinine to micromoles per liter (μmol/L), multiply by 88.4.

In the subset of patients with CrCl ≤ 40 mL/Min and/or SCr ≥2.0 mg/dL, no cases of CIN (0/39) were detected after the administration of iomeprol-400, independently of the CIN endpoint used. In this subset of patients at higher risk, the rate of CIN after iodixanol-320 was 11.8% (4/34) using the primary endpoint, and 5.9% (2/34) using the secondary CIN endpoints (Table 3).

No CIN cases required dialysis. Follow-up SCr values at 7 days were available for 3 of the 5 patients who experienced an increase in SCr ≥0.5 mg/dL at 48 to 72 hours after the administration of iodixanol-320. In those patients, SCr levels remained elevated over baseline levels by 0.6, 0.9, and 1.2 mg/dL. Further details about the 5 patients who developed CIN are given in Table 4.

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 did not demonstrate a significant relationship between the occurrence of CIN and age, gender, race, diabetes mellitus, dose by body weight, baseline SCr, volume supplementation, and concomitant use of potentially nephrotoxic medications. No significant treatment effect was evident between the 2 contrast agent groups.

After contrast administration, the mean SCr level fell slightly in the iomeprol-400 group (−0.04 ± 0.19 mg/dL), whereas it rose slightly in the iodixanol group (0.06 ± 0.27 mg/dL) (Table 5). The difference in mean change in SCr between the 2 groups was statistically significant ($P = 0.017$).

DISCUSSION

The type of the CM is an important factor in determining the risk of CIN in patients with impaired renal function. In a meta-analysis of 24 randomized comparative trials, Barrett and Carlisle[15] showed that the incidence of CIN in

TABLE 2. Incidence of Contrast-Induced Nephropathy (CIN)—All Patients (N = 148)

CIN Endpoint	Iomeprol-400 (N = 76)	Iodixanol-320 (N = 72)	95% Confidence Interval	P*
Postcontrast increase in SCr ≥0.5 mg/dL (44.2 μmol/L)	0	5 (6.9%)	(−12.8%, −1.1%)	0.025
Postcontrast increase in SCr ≥25%	4 (5.3%)	5 (6.9%)	(−9.4%, 6.0%)	0.74
Postcontrast decrease in CrCl ≥25%	1 (1.3%)	2 (2.8%)	(−6.0%, 3.1%)	0.61

*Fisher exact test.

TABLE 3. Incidence of Contrast-Induced Nephropathy (CIN)—Patients With Creatinine Clearance ≤40 mL/Min and/or SCr ≥2.0 mg/dL (N = 73)

CIN Endpoint	Iomeprol-400 (N = 39)	Iodixanol-320 (N = 34)	95% Confidence Interval	P*
Postcontrast increase in SCr ≥0.5 mg/dL (44.2 μmol/L)	0	4 (11.8%)	(−22.6%, −0.93%)	0.04
Postcontrast increase in SCr ≥25%	0	2 (5.9%)	(−13.8%, 2.03%)	0.21
Postcontrast decrease in CrCl ≥25%	0	2 (5.9%)	(−13.8%, 2.03%)	0.21

*Fisher exact test.

TABLE 4. History and Clinical Outcome of Patients With Contrast-Induced Nephropathy

Patient Age, Sex, Contrast Agent	Medical History	Drug Prophylaxis, Hydration	Baseline SCr, Baseline ClCr	Postdose SCr, Postdose CrCl	SCr at 7 Days Postdose
82 yr, male, Iodixanol-320	Arterial hypertension, chronic renal failure, prostatic neoplasm	N-Acetylcysteine, 2000 mL IV of 0.9% NaCl solution	2.5 mg/dL (220.5 μmol/L), 19.2 mL/Min/1.73 m^2	3.1 mg/dL (273.4 μmol/L), 15.5 mL/Min/1.73 m^2	NA
56 yr, male, Iodixanol-320	Medullary sponge kidney, diabetes mellitus, chronic renal failure	None, 1000 mL IV of 0.9% NaCl solution + 500 mL IV of 5% dextrose solution	1.6 mg/dL (141.1 μmol/L), 49.1 mL/Min/1.73 m^2	2.1 mg/dL (185.2 μmol/L), 37.4 mL/Min/1.73 m^2	2.8 mg/dL (247.0 μmol/L), 28.0 mL/Min/1.73 m^2
71 yr, female, Iodixanol-320	None significant	None, 1000 mL IV of 0.9% NaCl solution	1.1 mg/dL (97.0 μmol/L), 36.7 mL/Min/1.73 m^2	1.7 mg/dL (149.9 μmol/L), 23.5 mL/Min/1.73 m^2	NA
72 yr, male, Iodixanol-320	Prostatic cancer, chronic renal failure	None, not performed	2.4 mg/dL (211.7 μmol/L), 27.3 mL/Min/1.73 m^2	4.1 mg/dL (361.6 μmol/L), 16.0 mL/Min/1.73 m^2	3.0 mg/dL (264.6 μmol/L), 21.8 mL/Min/1.73 m^2
53 yr, male, Iodixanol-320	Hypertension, chronic renal failure	None, 2000 mL IV of 0.9% NaCl solution + 2000 mL IV of 5% dextrose solution	4.7 mg/dL (414.4 μmol/L), 18.0 mL/Min/1.73 m^2	5.6 mg/dL (493.9 μmol/L), 15.1 mL/Min/1.73 m^2	5.6 mg/dL (493.9 μmol/L), 15.1 mL/Min/1.73 m^2

patients at risk was significantly higher after the administration of high-osmolal CM (osmolality >1500 mOsm/kg) than after low-osmolal CM (LOCM, osmolality <915 mOsm/kg). Today, all guidelines recommend to avoid the use of high-osmolal CM in patients at increased risk for CIN. The question has been as to whether the other available CM, either LOCM or iso-osmolar CM (IOCM, osmolality 290 mOsm/kg) differ in their nephrotoxic potential. A number of studies have compared iodixanol with LOCM in high-risk patients receiving intra-arterial injections of contrast for cardiac or peripheral angiography procedures.[16–21] Presented in Tables 6 (all patients) and 7 (diabetic patients) are the design and results of the head-to-head comparisons of the IOCM iodixanol with LOCM following their intra-arterial administration in renally impaired patients. Significant differences have been observed in only 2 studies in which the LOCM were iohexol and ioxaglate.[17,18] In the RECOVER study, however, significant differences were observed only when the 2 endpoints, SCr increases ≥0.5 mg/dL or 25% from baseline, were combined.[18] A retrospective survey of outcomes from a Swedish registry study involving over 55,000 patients showed that patients receiving iodixanol were twice as likely to experience clinically significant acute renal failure as those receiving ioxaglate.[22] Differences in risk of developing CIN following iohexol and ioxaglate compared with the IOCM iodixanol were suggested by a pooled analysis conducted by McCullough et al[23] on a database of iodixanol clinical studies maintained by GE Healthcare. The aim of that pooled analysis was to compare changes in SCr and CIN rates in patients receiving the IOCM versus several types of LOCM. Most of the patients in the LOCM group were exposed to ioxaglate (58.7%) or iohexol (28.3%). The remaining patients received iopromide (Ultravist®, Bayer-Schering Pharmaceuticals, Berlin, Germany; 7.9% of patients in the analysis) or iopamidol (5.1%). The overall results of the analysis showed a reduced risk of CIN with the IOCM, though the only 2 studies with the LOCM iopromide and iopamidol in the analysis showed an effect favoring the LOCM, with CIN experienced only by

the patients who had received iodixanol. In essence, the meta-analysis by McCullough et al suggested that iodixanol may be less nephrotoxic than iohexol and ioxaglate, but could not show that the IOCM was less nephrotoxic than the LOCM iopamidol and iopromide. Solomon and and DuMouchel[24] published a systematic review of prospective, randomized, controlled studies of CIN in renally impaired patients receiving intra-arterial doses of iodixanol or other LOCM, and conducted a meta-analysis of the data from those studies to determine whether the osmolality of CM was predictive of CIN incidence. A multivariate logistic regression model showed that the risk of CIN was similar with the IOCM iodixanol and the LOCM iopamidol, and lower with both iodixanol and iopamidol compared with iohexol. Similar analyses and results had been previously reported by Solomon[25] and Sharma and Kini.[26]

TABLE 5. Changes in Serum Creatinine and Creatinine Clearance From Baseline

	Iomeron-400 (N = 76)	Visipaque-320 (N = 72)	P*
Serum creatinine (mg/dL)**			
Baseline	1.7 ± 0.60	1.7 ± 0.73	0.87
Postcontrast (48–72 h)	1.7 ± 0.58	1.8 ± 0.84	
Change from baseline	−0.04 ± 0.19	0.06 ± 0.27	0.02
Creatinine clearance (mL/Min)			
Baseline	41.5 ± 13.1	43.0 ± 13.3	0.49
Postcontrast (48–72 h)	42.1 ± 13.0	42.8 ± 14.8	
Change from baseline	0.61 ± 5.3	−0.22 ± 6.4	0.43

*Unpaired *t* test was used to test for differences in baseline values of serum creatinine and creatinine clearance. Mean changes from baseline were analyzed using analysis of covariance (ANCOVA), using the predose SCr measurement as covariate.

**To convert values for serum creatinine to micromoles per liter (μmol/L), multiply by 88.4.

The absence of a significant difference in CIN rate between LOCM iopamidol and IOCM iodixanol was also found in a prospective, randomized, double-blind study (the IMPACT study) of the effects of the IV administration of a relatively high dose (40 gI) of the 2 agents in 155 patients with moderate-to-severe CKD (CrCl <60 mL/Min).[27] In this study, the rate of CIN, defined as an absolute increase in SCr ≥0.5 mg/dL (44.2 μmol/L) was 2.6% (2/76) after iodixanol, whereas no cases of CIN (0/77) were observed in the iopamidol group. Similarly, no cases of CIN were observed after the administration of an IV dose of 40 gI of the LOCM iomeprol in the ACTIVE study, whereas 5 patients (6.9%) developed CIN with the same dose IOCM iodixanol, despite the higher proportion of patient suffering from diabetes mellitus in the iomeprol group.

In the IMPACT study, CIN was observed in 2/7 (28.5%) patients with SCr ≥2.0 mg/dL (>176.8 μmol/L) after iodixanol and in none of those high-risk patients (0/11) given iopamidol. Similarly, in the ACTIVE study, no cases of CIN (0/39) were observed after the administration of iomeprol-400 in patients with CrCl ≤40 mL/Min and/or SCr ≥2.0 mg/dL, whereas the rate of CIN in these high-risk patients was as high as 11.6% (4/34) after iodixanol. However, no significant differences in relative SCr rises of ≥25% from baseline or CrCl decreases of ≥25% were observed in both the IMPACT and the ACTIVE studies, so that the clinical significance of the observed differences between LOCM and IOCM may be limited to the population with more severe impairment of renal function.

Two other studies have compared iodixanol with LOCM after IV administration of contrast in risk patients.[28,29] Carraro et al[28] conducted a prospective, randomized, double-blind comparison of iodixanol with iopromide (Ultravist®, Bayer Healthcare) in 64 patients with moderate-to-severe renal insufficiency undergoing excretory urography. Renal function was assessed before and 1, 6, 24, and 48 hours, and 7 days after the contrast-enhanced examination.

TABLE 6. Clinical Trials Comparing Iodixanol with LOCM Following Intra-arterial Administration: Total Study Population

Publication	Study Agents	Study Design	Patient Population	CIN Endpoint*	CIN Rates
Chalmers and Jackson[16]	Iodixanol-270, iodixanol-300, iohexol-300	Prospective, open label, randomized	102 (54/48) patients with SCr >1.7 mg/dL	SCr increase ≥25% from baseline	Iodixanol 3.7%; iohexol 10.0% (*P* = ns)
Aspelin et al[17]	Iodixanol-320, iohexol-350	Prospective, double-blind, randomized	129 (64/65) patients with diabetes and SCr >1.5 mg/dL or CrCl <60 mL/Min	SCr increase ≥0.5 mg/dL from baseline	Iodixanol 3.1%, iohexol 26.1% (*P* = 0.002)
Jo et al[18]	Iodixanol-320, ioxaglate-320	Prospective, double-blind, randomized	275 (140/135) patients with CrCl ≤60 mL/Min	SCr increase ≥25% and/or ≥0.5 mg/dL from baseline	Iodixanol 7.9%, ioxaglate 17.0% (*P* = 0.02)
				SCr increase ≥0.5 mg/dL from	Iodixanol 3.6%, ioxaglate 8.9% (*P* = ns)
Solomon et al[19]	Iodixanol-320, iopamidol-370	Prospective, double-blind, randomized	414 (210/204) patients with eGFR <60 mL/Min	SCr increase ≥0.5 mg/dL from baseline	Iodixanol 6.7%, iopamidol 4.4% (*P* = ns)
Jingwei et al[20]	Iodixanol, iopamidol	Prospective, not randomized, open label	87 (46/41) patients with CrCl <60 mL/Min	SCr increase ≥25% and/or ≥0.5 mg/dL from baseline	Iodixanol 10.9%, iopamidol 12.2% (*P* = ns)
Briguori et al[21]	Iodixanol-320, iobitridol-350	Retrospective	225 (110/115) patients with SCr >1.5 mg/dL or CrCl <60 mL/Min	SCr increase ≥0.5 mg/dL from baseline	Iodixanol 2.7%, iobitridol 3.5% (*P* = ns)

*A serum creatinine (SCr) increase ≥0.5 mg/dL corresponds to an SCr increase ≥44.2 μmol/L.

TABLE 7. Clinical Trials Comparing Iodixanol with LOCM Following Intra-arterial Administration: Patients With Renal Insufficiency and Diabetes Mellitus

Publication	Study Agents	Study Design	Patient Population	CIN Endpoint*	CIN Rates
Aspelin et al[17]	Iodixanol-320, iohexol-350	Prospective, double-blind, randomized	129 (64/65) patients with diabetes and SCr >1.5 mg/dL or CrCl <60 mL/Min	SCr increase ≥0.5 mg/dL from baseline	Iodixanol 3.1%, iohexol 26.1% (P = 0.002)
Jo et al[18]	Iodixanol-320, ioxaglate-320	Prospective, double-blind, randomized	97 (48/49) patients with diabetes and CrCl ≤60 mL/Min	SCr increase ≥25% and/or ≥0.5 mg/dL from baseline	Iodixanol 10.4%, ioxaglate 26.5% (P = 0.04)
				SCr increase ≥0.5 mg/dL from baseline	Not reported
Solomon et al[19]	Iodixanol-320, iopamidol-370	Prospective, double-blind, randomized	170 (92/78) patients with diabetes and eGFR <60 mL/Min	SCr increase ≥0.5 mg/dL from baseline	Iodixanol 13.0%, iopamidol 5.1% (P = ns)
Briguori et al[21]	Iodixanol-320, iobitridol-350	Retrospective	104 (55/49) patients with diabetes and SCr >1.5 mg/dL or CrCl <60 mL/Min	SCr increase ≥0.5 mg/dL from baseline	Iodixanol 5.5%, iobitridol 4.1% (P = ns)

*A serum creatinine (SCr) increase ≥0.5 mg/dL corresponds to an SCr increase ≥44.2 μmol/L.

TABLE 8. Clinical Trials Comparing Iodixanol with LOCM Following Intravenous Injection to Patients With Renal Insufficiency

Publication	Study Agents	Study Design	Patient Population	CIN Endpoint*	CIN Rates
Barrett et al[27]	Iodixanol-320, iopamidol-370	Prospective, double-blind, randomized	153 (76/77) patients with SCr >1.5 mg/dL or CrCl <60 mL/Min	SCr increase ≥0.5 mg/dL from baseline	Iodixanol 2.6%, iopamidol 0.0% (P = ns)
Carraro et al[28]	Iodixanol-320, iopromide-300	Prospective, double-blind, randomized	64 (32/32) patients with SCr >1.5 mg/dL and <3.0 mg/dL	SCr increase ≥50% from baseline	Iodixanol: 3.1%, iopromide 0.0% (P value not reported)
Kolehmainen and Soiva[29]	Iodixanol-320, iobitridol-350	Prospective, double-blind, randomized	50 (25/25) with renal impairment	SCr increase ≥0.5 mg/dL from baseline	Iodixanol 16.0%, iobitridol 16.0% (P = ns)
ACTIVE study	Iodixanol-320, iomeprol-400	Prospective, double-blind, randomized	148 (72/76) patients with SCr >1.5 mg/dL or CrCl <60 mL/Min	SCr increase ≥0.5 mg/dL from baseline	Iodixanol 6.9%, iomeprol 0.0% (P = 0.025)

*A serum creatinine (SCr) increase ≥0.5 mg/dL corresponds to an SCr increase ≥44.2 μmol/L.

One nondiabetic patient in the iodixanol group developed CIN (SCr increasing from 2.5 to 5.4 mg/dL, ie, 220.5 to 476.3 μmol/L in 24 hours, returning to baseline by the 48-hour evaluation), whereas no CIN cases were observed in the iopromide group. Using the same study design, Kolehmainen et al[29] compared iodixanol with the LOCM iobitridol in 50 patients with severe CKD undergoing cranial or body CT procedures. Both groups received similar volumes of contrast (113.3 mL of iobitridol, 112.7 mL of iodixanol), and had similar baseline values of SCr (2.7 mg/dL, ie, 238.7 μmol/L in the iobitridol group, 2.6 mg/dL, ie, 229.8 μmol/L in the iodixanol group) and CrCl (28.7 mL/min vs. 27.5 mL/min). The incidence of increases in SCr ≥0.5 mg/dL (44.2 μmol/L) was 17% with both agents, whereas a decrease in CrCl ≥25% was observed in 12.5% of the patients with both agents.

Reported in Table 8 are the design and results of the 4 CIN studies aimed at comparing iodixanol and LOCM after their IV administration to patients with renal insufficiency, the ACTIVE study included. Overall, the results of clinical trials other than the NEPHRIC study and the RECOVER study failed to support the benefit of the isotonic dimer iodixanol over LOCM. Iodixanol has shown a reduced CIN rate only in 2 studies in which it was compared against the nonionic monomer iohexol or the ionic dimer ioxaglate. No differences in CIN rates have ever been observed between iodixanol and the LOCM iopamidol, iopromide and iobitridol. Because the osmolality of iohexol and ioxaglate is similar to that of iopamidol, iopromide, and iobitridol, the available evidence does not provide any substantive support to the hypothesis that the osmolality of LOCM plays an important role in CIN pathogenesis. The ACTIVE study provides additional support to the absence of clinical benefit deriving from the selective use of iodixanol in renally impaired patients.

STUDY LIMITATIONS

The ACTIVE trial provides safety data on 148 evaluable patients, which is more than that contained in the NEPHRIC study (129 evaluable patients).[17] Like that study, using the same CIN endpoint of increases in SCr equal or greater than 0.5 mg/dL from baseline, the ACTIVE study shows a significant treatment effect favoring one of the

contrast agents evaluated. Therefore, although this was a relatively small study, we consider the ACTIVE study a valid addition to the literature on this important topic and do not feel sample size is a significant limitation of this study.

Two studies have reported worsening of renal function in inpatients undergoing unenhanced CT.[30,31] Although these studies were not blinded nor randomized, were performed in a limited subset of patients with pre-existing renal impairment, and were aimed at detecting severe cases of postcontrast acute renal failure (50% increase in SCr or greater), the studies did show the potential for noncontrast-related worsening of renal function. The absence of a control group in the ACTIVE study may have affected the possibility to judge the true nephrotoxic potential of the IV administration of iodixanol and iomeprol in risk patients. The absence of increases in SCr equal to or above 0.5 mg/dL in the iomeprol group, however, limits the potential for incorrect interpretation of the study results.

Similar to the IMPACT study, patients with changing kidney function before contrast were excluded from the CIN analysis. The definition of "stable" renal function in the ACTIVE study was based on a blinded review of clinical trial data by the Renal Safety Review Board. The qualifying SCr levels were drawn at various timepoints in the days immediately before the baseline sample, and the reviewers considered that a change of ≤3% per day reflected an appropriate criterion for stable kidney function. The definition of "stable" kidney function was arbitrary, but it was prospectively defined and used by Renal Safety Review Board to review each patient's data before unblinding, and none of the patients excluded from the analysis experienced CIN by any definition used in this study.

CONCLUSIONS

The incidence of CIN was significantly higher after the IV administration of iodixanol-320 than iomeprol-400 in patients with moderate-to-severe CKD. The mean increase in SCr from baseline was also higher in patients receiving iodixanol. Characteristics of the individual contrast agents other than osmolality may be important in causing nephrotoxicity.

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APPENDIX: INVESTIGATORS IN THE ABDOMINAL COMPUTED TOMOGRAPHY: IOMERON® 400 VERSUS VISIPAQUE™ 320 ENHANCEMENT (ACTIVE) TRIAL

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