

Nephrotoxicity of iodixanol versus iopamidol in patients with chronic kidney disease and diabetes mellitus undergoing coronary angiographic procedures

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Background The choice of radiographic contrast media for use in patients at increased risk of contrast-induced nephropathy (CIN) is of ongoing interest.

Methods The current study is a prospective, multicenter, randomized, double-blind design comparing the renal effects of the non-ionic, iso-osmolal agent, iodixanol, versus the non-ionic, low-osmolal agent, iopamidol, in 526 subjects with impaired baseline renal function (chronic kidney disease) and diabetes mellitus undergoing diagnostic and/or therapeutic coronary angiographic procedures. The co-primary end points were the peak increase in serum creatinine (SCr) and the incidence of CIN (increase ≥ 0.5 mg/dL) in SCr from baseline within 3 days of receiving contrast media.

Results In 418 evaluable subjects with complete postcontrast media SCr data, the median peak increase in SCr in the iodixanol arm was 0.10 mg/dL, whereas in the iopamidol arm, the median peak increase was 0.09 mg/dL ($P = .13$). The overall CIN incidence was 10.5% (11.2% in the iodixanol arm and 9.8% in the iopamidol arm, $P = .7$). The volume of contrast media, volume of saline administered, frequency of coronary interventional procedures, and severity of baseline kidney disease and of diabetes mellitus were similar between treatments.

Conclusions In the present study, the overall rate of CIN in patients with chronic kidney disease and DM undergoing coronary angiographic procedures was 10.5%. There was no significant difference between iodixanol and iopamidol in either peak increase in SCr or risk of CIN. (Am Heart J 2009;158:822-828.e3.)

Contrast-induced nephrotoxicity (CIN) is defined as acute deterioration in renal function within 72 hours in patients receiving radiographic contrast media.¹⁻³ Risk factors identified for CIN represent a constellation of clinical- and procedure-specific variables.⁴⁻⁷ Contrast-induced nephrotoxicity is the third most common cause of acute renal failure in hospitalized patients,⁸⁻¹⁰ increas-

ing both short-term¹¹⁻¹³ and long-term¹²⁻¹⁴ risk for adverse outcomes. Identification of high-risk patients and mitigation of the risk of CIN have become important, and interrelated, issues in cardiovascular medicine.^{5,15-17}

Although general agreement exists about the benefit of low-osmolal contrast media for CIN prevention in subjects at risk,¹⁸⁻²¹ debate on interspecies differences in CIN risk among available low-osmolal agents²²⁻²⁵ as well as differences between iso-osmolal and low-osmolal contrast media continue to motivate research.²⁶ The current study is a multicenter, randomized, double-blind, parallel-group study comparing the renal effects of the iso-osmolal agent, iodixanol (Visipaque, GE Healthcare, Princeton, NJ), with the low-osmolal agent, iopamidol (Isovue, Bracco Diagnostics, Inc., Princeton, NJ), in subjects with diabetes mellitus (DM) and impaired renal function (chronic kidney disease [CKD]) undergoing coronary angiography with or without percutaneous coronary intervention.

Methods

Trial organization and conduct

Fifty-three centers enrolled at least 1 subject (29 centers in Europe, 21 centers in North America, and 3 centers in India).

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Trial registration at clinicaltrials.gov: NCT00209430.

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Table I. Study inclusion and exclusion criteria

Inclusion criteria:

1. The subject was older than 18 y.
2. The subject was referred for coronary angiography with or without percutaneous coronary intervention.
3. The subject had DM I or II, treated with insulin or oral antiglycemics for at least 1 y.
4. The subject had renal impairment of non-acute etiology: SCr measurement not older than 6 m $\geq 150 \mu\text{mol/L}$ (1.7 mg/dL) for men and $\geq 133 \mu\text{mol/L}$ (1.5 mg/dL) for women or a creatinine clearance $\leq 50 \text{ mL/min}$ calculated according to Cockcroft-Gault formula shown below: (F_G : 1 for males and 0.85 for females; body weight: to convert from pounds to kilograms, divide body weight by factor 2.205; SCr, to convert milligrams per deciliter to micromole per liter, multiply SCr with factor 88.4)

$$\text{CrCl}_{(\text{ml/min})} = \frac{(140 - \text{age}_{\text{years}}) \times \text{bodyweight}_{(\text{kg})} \times 1.23 \times F_G}{\text{SCr}_{(\mu\text{mol/l})}}$$

5. The subject was able and willing to comply with study procedures including hydration protocol, and signed and dated (ie, date and time) informed consent was obtained.
6. The subject was male, or a female who was either surgically sterile (had had a documented bilateral oophorectomy and/or documented hysterectomy), postmenopausal (cessation of menses for $>1 \text{ y}$), or nonlactating, or if of childbearing potential the results of a serum or urine human chorionic gonadotropin pregnancy test, performed at screening, with the result known before contrast media administration, was negative.

Exclusion criteria:

1. The subject was previously included in the study.
2. The subject had participated in any contrast media study within 30 d before study enrolment.
3. The subject had received iodinated contrast medium within 7 d before study agent administration or was scheduled to receive one within the study period.
4. The subject was planned to undergo major surgery (coronary artery bypass graft, carotid endarterectomy, vascular surgery) within 3 d after the contrast media administration.
5. The subject was planned to undergo selective renal angiography.
6. The subject had a history of serious hypersensitivity reaction to iodinated contrast media.
7. The subject had severe liver or hematologic disease, multiple myeloma, or manifest thyrotoxicosis.
8. The subject had severe heart failure requiring intravenous therapy with diuretics, inotropes, and/or vasodilators.
9. The subject was planned to receive an intravenous diuretic or intravenous mannitol in connection to the contrast media administration.
10. The subject was hemodynamically unstable prestudy (ie, inability to sustain systolic blood pressure $>90 \text{ mm Hg}$ within 48 h before contrast media administration without pressor or balloon support).
11. The subject was on hemodialysis or peritoneal dialysis, and/or was in acute renal failure.
12. The subject had undergone kidney transplantation.
13. The subject had received or would receive any of the following potentially nephroprotective drugs within 3 d before or 3 d after contrast media administration; *N*-acetylcysteine, fenoldopam, dopamine or hydration with sodium bicarbonate. Potentially nephroprotective drugs such as Ca-channel blockers, theophylline, etc, were allowed provided they were used for treatment of the subject's chronic underlying disease.
14. The subject had received or was planned to receive any of the following nephrotoxic drugs within 7 d before or 3 d after contrast media administration; aminoglycosides, vancomycin, amphotericin B, cyclosporin, methotrexate, cisplatin.
15. The subject had received or was planned to receive nonsteroidal anti-inflammatory drugs within 3 d before or 3 d after contrast media administration, with the exception of low doses of acetyl salicylic acid (up to 325 mg/d, and at a single occasion in connection with percutaneous

Table I (continued)

- coronary intervention up to 500 mg). However, subjects who were on a stable nonsteroidal regimen could be enrolled.
16. The subject had or was planned to have the initiation, discontinuation, or change in dose within 3 d before or 3 d after contrast media administration of any of the following: trimethoprim, cimetidine, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers.
 17. The subject was on metformin (eg, Glucophage, Bristol-Meyers-Squibb, New York, NY) at the time of coronary angiography/intervention. Metformin had to be discontinued according to local guidelines, and stopped no later than the time of CM administration, withheld for at least 48 h, until the subject's SCr had been evaluated and it was deemed safe to resume metformin.

Details of all study centers, investigators, number of subjects enrolled, and administered contrast media are listed in Appendix A. Each subject gave written informed consent before any procedures or assessments and after the aims, methods, anticipated benefits, and potential hazards were explained.

This study was conducted in accordance with the Declaration of Helsinki, the Good Clinical Practice Consolidated Guideline approved by the International Conference on Harmonization and applicable national, and local laws and regulations.

Study population

Inclusion and exclusion criteria are detailed in Table I. Study subjects had both currently treated type I or type II DM and CKD of non-acute etiology and were scheduled for coronary angiography with or without percutaneous coronary intervention. Chronic kidney disease was defined as serum creatinine (SCr) $\geq 1.7 \text{ mg/dL}$ for men and $\geq 1.5 \text{ mg/dL}$ for women or a creatinine clearance $\leq 50 \text{ mL/min}$, as estimated by the Cockcroft-Gault formula at screening. The screening creatinine value was not to be older than 6 months and was used solely to determine study eligibility.

Study protocol

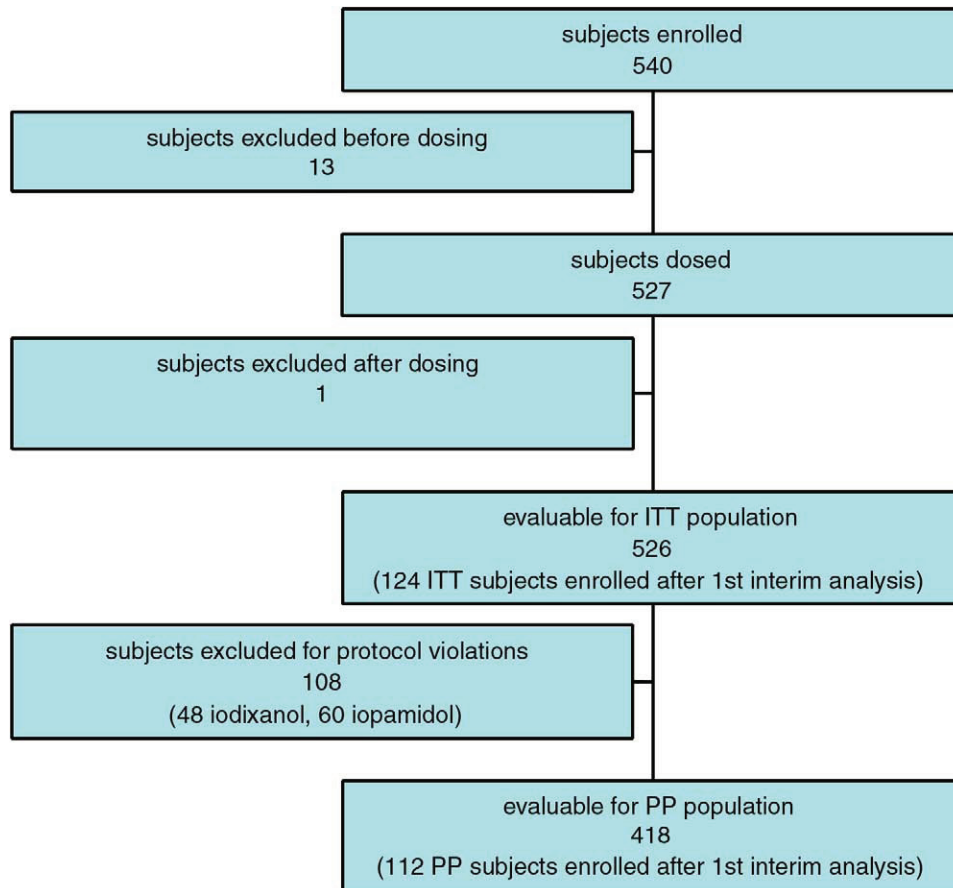
The baseline period was defined as the interval from 72 hours before contrast media administration to the time of administration of the study agent. Subjects were randomized to receive either iodixanol (290 mOsm/kg H_2O ; 320 mgI/mL) or iopamidol (796 mOsm/kg H_2O ; 370 mgI/mL). Each subject underwent coronary angiography with or without percutaneous coronary intervention according to the standard of care at the center.

Contrast media volumes varied between individuals according to medical need. Subjects, and site personnel evaluating the subjects, were blinded to the contrast media administered. All subjects were hydrated before, during, and after the procedure, as previously described.²⁷

Venous blood was drawn for SCr concentration determination before starting intravenous hydration (baseline), and 2, 3, and 7 days after the procedure. Serum creatinine changes from baseline after contrast media administration were evaluated. Samples were analyzed at a central laboratory.

Additional safety assessments included the recording of adverse events up to 7 days post-contrast media administration.

Figure 1



Disposition of subjects in the current study.

Statistical design and determination of sample size

The study design specified 2 co-primary end points:

1. Maximum SCr value through day 3 compared to baseline.
2. Incidence of CIN, defined as the proportion of evaluable subjects with a SCr increase of at least 0.5 mg/dL from baseline up to day 3.

The sample size was estimated on the co-primary end point incidence of CIN, defined as the number of subjects with a SCr increase of at least 0.5 mg/dL (44 μ mol/L) from baseline (prehydration) up to day 3. The estimated CIN incidence in the iodixanol group was based on available data reporting CIN rates between 3% and 11% in the population with both DM and CKD.^{28,29} The CIN rate in the iopamidol group was based on published data on the subgroup with DM and CKD where the reported incidences of CIN ranged between 9% and 30%.³⁰⁻³³ A sample size of 408 evaluable subjects gave 90% power to detect a significant difference in CIN rates between the iodixanol group (expected CIN rate, 6%) and the iopamidol group (expected CIN rate, 16%) at a significance level of .05. Accounting for a 10% nonevaluable rate, the total number of subjects included in the study was estimated to be 450.

Two analysis populations were defined (Figure 1):

1. Intention-to-treat (ITT) population: all study subjects who received one of the contrast media.
2. Per-protocol (PP) population: all subjects complying with the protocol sufficiently to ensure that the data would be likely to exhibit the effects of contrast media, that is, all subjects with a precontrast (baseline) and at least 1 postcontrast SCr value on day 2 or 3, without presence of any major protocol violations. The most common exclusion reasons were unauthorized concomitant medication (40%), baseline blood sample taken after starting hydration (30%), blood sample missing (25%), and low contrast media volume (<20 mL) (5%).

An adjudication committee of 5 investigators blinded to treatment assignment evaluated all subjects in the PP population who reached the prespecified CIN definition. If review of an individual case led to consensus that a cause other than contrast media could be implicated in the SCr increase, the subject was excluded from the above group of all patients manifesting an increase in SCr of >0.5 mg/dL, and the results recalculated as a more conservative CIN rate.

Table II. Baseline demographic characteristics

Variable	ITT population			PP population			
	Total n = 526	Iodixanol n = 263	Iopamidol n = 263	Total n = 418	Iodixanol n = 215	Iopamidol n = 203	
Gender	Male	351 (67%)	177 (67%)	174 (66%)	270 (65%)	139 (65%)	131 (65%)
	Female	175 (33%)	86 (33%)	89 (34%)	148 (35%)	76 (35%)	72 (35%)
Race	White	386 (73%)	189 (72%)	197 (75%)	307 (73%)	156 (73%)	151 (74%)
	Black	31 (6%)	22 (8%)	9 (3%)	22 (5%)	16 (7%)	6 (3%)
	Oriental/Asian	91 (17%)	45 (17%)	46 (17%)	76 (18%)	39 (18%)	37 (18%)
	Other	18 (3%)	7 (3%)	11 (4%)	13 (3%)	4 (2%)	9 (4%)
Age (y)	Mean	69.7	69.5	69.8	69.6	69.6	69.7
	SD	8.8	8.7	8.9	8.9	8.7	9.2
	Range (min-max)	41-87	42-87	41-87	41-87	42-87	41-87
BMI (kg/m ²)	Mean	29.0	28.9	29.1	28.8	28.8	28.8
	SD	6.3	6.0	6.5	6.1	6.0	6.1
	Range (min-max)	16-71	17-60	16-71	17-60	17-60	16-50

ITT and PP populations defined in Methods (see text for details).

The primary analyses were based on data pooled across all centers. Categorical variables were summarized by counts/percentage and continuous variables by mean and SDs for normally distributed data and median and interquartile range (IQR) for non-gaussian data. Tabulations of summary statistics, graphical presentations, and statistical analyses were performed using SAS software. A *P* value of $\leq .05$ was considered statistically significant. 95% CIs for differences are reported, where appropriate.

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Results

The study was conducted between August 25, 2005, and February 26, 2007.

Clinical characteristics of study population

Figure 1 illustrates the final patient disposition. Two hundred two patients in the PP population were from Europe (iodixanol, 103; iopamidol, 99), 147 from North American (iodixanol, 76; iopamidol, 71), and 69 from India (iodixanol, 36; iopamidol, 33). There were no significant differences in contrast media allocation over these geographic regions.

Table II summarizes the clinical and demographic variables. There were no significant differences between treatments, in either the ITT or PP populations, in any of these baseline factors. In addition, there were no significant differences in DM severity, type, or duration (for ITT: iodixanol 12.8 ± 9.5 years, iopamidol 13.4 ± 10.1 years, *P* = .48; for PP: iodixanol 12.5 ± 10.0 years; iopamidol 13.9 ± 11.0 years, *P* = .17) between treatments (Table III).

There were no significant differences in the median baseline SCr (iodixanol 1.60 mg/dL, IQR 0.6 mg/dL;

Table III. Severity and duration of DM

	n	Type of DM		Duration		
		Type I n (%)	Type II n (%)	n	Mean (y)	SD
ITT population						
Total	526	22 (4)	504 (96)	522	13.1	9.8
Iodixanol	263	11 (4)	252 (96)	262	12.8	9.5
Iopamidol	263	11 (4)	252 (96)	260	13.4	10.1
PP population						
Total	418	20 (5)	398 (95)	415	13.2	10.0
Iodixanol	215	11 (5)	204 (95)	214	12.5	10.0
Iopamidol	203	9 (5)	194 (96)	201	13.9	11.0

iopamidol 1.51 mg/dL, IQR 0.7 mg/dL; *P* = .28) or median baseline CrCl (iodixanol 45.5 mL/min, IQR 22.1 mL/min; iopamidol 47.9 mL/min, IQR 22.1 mL/min; *P* = .8) between the PP treatment groups.

There were no significant differences between treatment groups in either the ITT or PP populations, in contrast media volume (for ITT: iodixanol 117.7 ± 77.4 mL, iopamidol 121.4 ± 85.1 mL, *P* = .55; for PP: iodixanol 121.1 ± 78.2 mL, iopamidol 112.6 ± 67.6 mL, *P* = .45). The amount of iodine administered (for ITT: iodixanol 37.7 ± 24.9 gI, iopamidol 44.9 ± 31.5 gI, *P* = .002; for PP: iodixanol 38.7 ± 25.0 gI, iopamidol 41.7 ± 25.0 gI, *P* = .002) was greater in the iopamidol group.

In the ITT population, 26% of patients receiving iodixanol and 27% of patients receiving iopamidol underwent coronary intervention. In the PP population, 27% of patients receiving iodixanol and 25% of patients receiving iopamidol underwent coronary intervention.

The mean hydration volumes (from 24 hours before until 72 hours after contrast media administration) were 1539 ± 1070 mL in the iodixanol group and 1447 ± 868 mL in the iopamidol group (*P* = .9).

Table IV. Measured SCr values over time

Treatment group	Observation time	Measured values (mg/dL)		
		n	Mean	SD
PP population				
Total (n = 418)	Baseline	418	1.64	0.53
	48 h	404	1.69	0.59
	72 h	396	1.69	0.62
	7 d	365	1.68	0.60
Iodixanol (n = 215)	Baseline	215	1.63	0.51
	48 h	209	1.70	0.58
	72 h	206	1.71	0.61
	7 d	187	1.69	0.60
Iopamidol (n = 203)	Baseline	203	1.64	0.56
	48 h	195	1.68	0.60
	72 h	190	1.68	0.62
	7 d	178	1.68	0.59

There were no differences between treatments in the proportion of patients with SCr determinations at any time point from baseline through day 3. Overall, ascertainment was 100% at baseline, 97% at 48 hours, and 95% at 72 hours (Table IV).

Renal outcomes: Primary end points

Mean/median peak SCr increased from baseline through day 3.

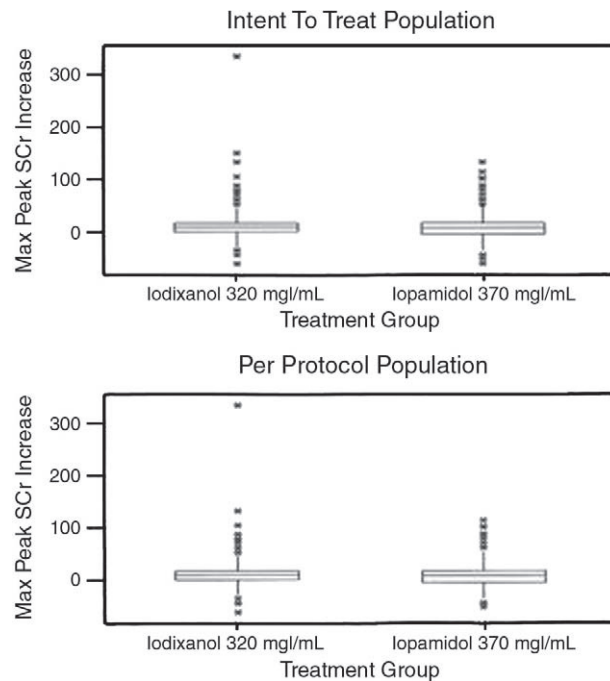
In the ITT population overall, the mean/median (IQR) peak SCr increase was $0.13 \pm 0.33/0.10$ mg/dL (0.20). The mean/median (IQR) peak SCr increase in the iodixanol ITT group was $0.14 \pm 0.38/0.10$ mg/dL (0.20) versus $0.11 \pm 0.28/0.09$ mg/dL (0.25) in the iopamidol ITT group ($P = .38$ by Wilcoxon rank sum test).

In the PP population overall, the mean/median (IQR) peak SCr increase was $0.11 \pm 0.33/0.10$ mg/dL (0.23). The mean/median (IQR) peak SCr increase with iodixanol was $0.14 \pm 0.38/0.1$ mg/dL (0.20) versus $0.09 \pm 0.26/0.09$ mg/dL (0.27) with iopamidol ($P = .13$ by Wilcoxon rank sum test). Figure 2 shows the distributions of the peak SCr increase through day 3 in each PP treatment arm.

Incidence of CIN from baseline up to day 3

There were 44 cases (10.5%) meeting the criterion of a SCr increase from baseline of, at least, $44 \mu\text{mol/L}$, or 0.5 mg/dL. The CIN rate with iodixanol was 11.2% (24/214) and 9.8% (20/203) with iopamidol. This difference was not statistically significant ($\chi^2 = 0.2$, $P = .7$) (95% CI -7.4% to +4.6%).

The adjudication committee evaluated all 44 cases before database lock to determine whether prespecified protocol deviations (eg, hydration amount or timing) or confounding (eg, subsequent hemodynamic deterioration or surgery) could be implicated in the SCr increase. Thirteen cases (4 iodixanol, 9 iopamidol) were so

Figure 2

Box and whisker plots of the maximum increase in SCr ($\mu\text{mol/L}$) through day 3 in the iodixanol (upper) and iopamidol (lower) PP treatment groups. The distributions are virtually superimposable with a median (IQR) peak increase in SCr of $9 \mu\text{mol/L}$ ($18 \mu\text{mol/L}$) in patients receiving iodixanol and $8 \mu\text{mol/L}$ ($24 \mu\text{mol/L}$) in patients receiving iopamidol ($1 \text{ mg/dL} = 88 \mu\text{mol/L}$).

identified. Thus, a more conservative CIN rate in the PP population overall was 7.4% (31 subjects) with 20 (9.3%) of 215 subjects receiving iodixanol and 11 (5.4%) of 203 subjects receiving iopamidol. This difference was not statistically significant ($\chi^2 = 2.3$, $P = .14$) (95% CI -1.2% to +8.9%).

There was no significant difference in CIN between patients undergoing percutaneous coronary intervention (iodixanol 10.5%, iopamidol 7.8%, $P = .13$) or angiography only (iodixanol 8.9%, iopamidol 4.6%, $P = .92$). When the PP population was categorized by contrast media volume administered (>80 or 100 mL vs <80 or 100 mL), again no differences in CIN between treatments were noted in either volume category. In patients with creatinine clearance <30 mL/min ($n = 42$), there were 3 instances of CIN in the 18 patients receiving iodixanol and 3 instances of CIN in the 24 patients receiving iopamidol ($P = .99$).

Overall safety profile

In the ITT population, 198 (38%) of 526 patients experienced a total of 437 adverse events. Thirty-one adverse events in 26 subjects were considered to be

treatment-related contrast media (17 events in 15 subjects receiving iodixanol, 14 events in 11 subjects receiving iopamidol). Most adverse events were mild in intensity and resolved during the study. There were 54 serious adverse events in 37 patients without identifiable differences between treatments in any category. Three subjects required either hemodialysis or hemofiltration. There were 7 in-hospital deaths in the ITT population (1.3%) and 3 deaths in the PP population (0.7%). Of the deaths in the PP population, there were no instances of CIN.

Discussion

In this study comparing the renal effects of the iso-osmolal agent, iodixanol, to the low-osmolal agent, iopamidol, in subjects with CKD and DM undergoing coronary angiographic procedures, there were no significant differences between contrast agents in the co-primary end points of peak increase in SCr through day 3 or CIN incidence through day 3. Both agents were well tolerated.

Contrast-induced nephropathy remains a major cause of acute kidney failure and is associated with short- and long-term cardiovascular morbidity and mortality. Consistent evidence in support of CIN prevention with pharmacologic treatments is lacking¹⁸ and the mainstays of CIN prevention remain volume repletion, that is, “hydration,” and the use of low or iso-osmolal contrast media.^{20,21} However, recent meta-analyses provide conflicting information, with one review suggesting the superiority of iodixanol²⁶ and another indicating no difference in renal safety between iso-osmolal and low-osmolal contrast media.³⁴ Data from recent clinical trials addressing CIN risk in the setting of coronary angiographic procedures indicate wide variation in risk^{27,35-40} with an overall CIN incidence, defined as a SCr increase of >0.5 mg/dL, of approximately 10%.

To date, only one trial has specifically examined the relative nephrotoxicity of iso-osmolal contrast media versus low-osmolal contrast media in patients with CKD and DM.²⁸ Our results differ from the latter, although the comparator in the current trial (iopamidol) differed from that in the latter (iohexol). Contrast-induced nephropathy risk in the iodixanol and iopamidol arms in the present trial were 11.2% and 9.8%, respectively, compared to 3% and 26% (in the iohexol arm), respectively. Despite study population differences, most notably the inclusion of only patients with CKD and DM in the present study, our results are similar to a recent trial comparing the relative nephrotoxicity of iodixanol versus iopamidol.³⁶ In the latter, comparably defined CIN rates with iodixanol and iopamidol were 6.7% and 4.4%, respectively ($P = .39$). The numerically higher overall CIN rate in the present study reflects the higher-risk patient population.

Varying CIN definitions have further confounded the issue of relative nephrotoxicities among low-osmolal

contrast media as well as between specific low-osmolal and iso-osmolal contrast media. In one trial, the difference between iodixanol and ioxaglate was significant only when CIN was defined as a SCr increase of $\geq 25\%$ or ≥ 0.5 mg/dL but not so when the ≥ 0.5 mg/dL criterion was applied.³⁷ Similarly, in another recent study³⁸ defining CIN as a SCr increase of $\geq 25\%$ or ≥ 0.5 mg/dL, the difference between iodixanol and iopromide was only marginally significant using the ≥ 0.5 mg/dL criterion. Thus, caution is needed when comparing studies in which the CIN definition varies among studies.

Sufficient prior data were available to estimate an expected CIN rate in subjects with CKD and DM exposed to iodixanol. The data available at the time of this study design were not, in retrospect, sufficiently reliable to estimate an expected CIN rate in subjects exposed to iopamidol. Significant overestimation of the latter, coupled with a modest underestimation of the expected rate with iodixanol, resulted in a significantly reduced (post hoc) power and sample size. It is also possible that, despite the recruitment of a “high-risk” group of patients, the evaluable subjects were “not sick enough.” A post hoc, subgroup analysis of the highest-risk candidates, those with creatinine clearance <30 mL/min and DM undergoing complex or emergent PCI, is limited by small subject numbers. In the present study, only 10% of patients had a creatinine clearance <30 mL/min. Finally, it may well be that there is no true difference in nephrotoxicity between iodixanol and iopamidol, or, if there is, such a difference is unlikely to be clinically meaningful.

In conclusion, in the present study, a significant difference in nephrotoxicity between the iso-osmolal contrast media iodixanol and the low-osmolal contrast media iopamidol in a high-risk patient population undergoing coronary angiographic procedures could not be demonstrated. Future clinical trial designs to address similar questions in even higher-risk populations (urgent/emergent procedures, poorly controlled/long-standing DM, creatinine clearance <30 mL/min) should carefully consider this body of prior evidence.

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Appendix A.

List of DXV405 investigators and subject enrollment

Center no.	Investigator/affiliation	No. of subjects enrolled*/given CM
001	Prof Peter Aspelin [†] /Karolinska University Hospital Huddinge, 141 86 Stockholm, Sweden	6/6
002	Dr Knut Endresen/Dept of Cardiology, Rikshospitalet University Hospital, Sognsvannsveien 20, 0027 Oslo, Norway	1/0
003	Dr Victor Legrand/Service de Cardiologie, Centre Hospitalier Universitaire, Domaine du Sart Tilman, 4000 Liège, Belgium	1/1
004	Dr Claude Hanet/Cliniques Universitaires St Luc, Service de Cardiologie, 10 avenue Hippocrate, 1200 Brussels, Belgium	0/0
005	PD Dr Willenbrock/Krankenhaus St Elisabeth und St Barbara, Klinik für Innere Medizin II, Mauerstrasse 5, Postfach 20 02 54, 06110 Halle (Saale), Germany	12/12
006	Dr Rainer Wessely Deutsches Herzzentrum München des Freistaates Bayern, Munich, Germany	4/4
007	Dr Marcus Wiemer/Herz- und Diabeteszentrum Nordrhein-Westfalen, Kardiologische Klinik, Georgstrasse 11, 32545 Bad Oeynhausen, Germany	29/27
008	Dr Rémi Sabatier/CHU Cote de Nacre, Service de Cardiologie, 14033 Caen Cedex, France	5/5
009	Prof Dr Ruth Strasser/Medizinische Klinik/Kardiologie, Technische Universität Dresden, Fetscherstrasse 76, 01307 Dresden, Germany	14/14
010	Dr Pierre Aubry/Hôpital Bichat, Service de Cardiologie B, 46, rue Henri Huchard, 75018 Paris, France	6/6
011	Dr Azfar Zaman/Freeman Hospital, Freeman Road, Newcastle NE7 7DN, UK	7/7
012	Centre withdrawn	–
013	Dr Thorsten Dill/Kerckhoff-Klinik GmbH, Benekestrasse 2-8, 61231 Bad Nauheim, Germany	9/9
014	Dr Eulogio García/Hospital Gregorio Marañón, Cardiology Dept, Doctor Esquerdo, 46, 28007 Madrid, Spain	4/4
015	Dr Francisco Fernández-Avilés/Hospital Universitario de Valladolid, Cardiology Dept, Avda Ramón y Cajal, 3, 47011 Valladolid, Spain	10/10
016	Dr Paolo Rubartelli/Ospedale Villascassi, Corso Scassi, 16126 Genova, Italy	5/5
017	Centre withdrawn	–
018	Dr Charles Knight/The London Chest Hospital, Bonner Road, Bethnal Green, London E2 9JX, UK	0/0

Appendix A (continued)

Center no.	Investigator/affiliation	No. of subjects enrolled*/given CM
019	Dr Joachim Schümmelfeder (until July 1, 2006), Dr Frank Gietzen (from July 1, 2006)/Herz- und Gefäss-Klinik GmbH, Salzburger Leite 1, 97616 Bad Neustadt/Saale, Germany	19/19
020	Prof Dr Franz-Josef Neumann/Herzzentrum Bad Krozingen, Am Südring 15, 79189 Bad Krozingen, Germany	14/14
021	Dr Jacques Boschat/CHU de Brest-Hôpital de la Cavale Blanche, Boulevard Tanguy Prigent, 29 200 Brest cedex, France	1/1
022	Dr Michael Rosseel/Algemeen Stedelijk Ziekenhuis, Cardiologie, Merestraat 80, 9300 Aalst, Belgium	0/0
023	Dr Marc Vincent/Brussels Heart Centre, Clinique Générale St Jean, 32 bd du Jardin Botanique, 1000 Brussels, Belgium	7/7
024	Dr Mathias Vrolix/ZOI-Campus St Jan, Cardiology department, Schiepsebos 6, 3600 Genk, Belgium	4/4
025	Prof Ludwig Thierfelder/Franz-Volhard-Klinik, Charité Campus Berlin-Buch, Wiltbergstrasse 50, 13125 Berlin, Germany	9/9
026	PD Dr Stefan Sack/Universitätsklinikum Essen, Zentrum für Innere Medizin, Klinik für Kardiologie, Westdeutsches Herzzentrum Essen, Hufelandstrasse 55, 45122 Essen, Germany	0/0
027	Dr Antonio Manari/Azienda Ospedaliera Arcispedale Santa Maria Nuova di Reggio Emilia, Struttura Complessa di Diagnostica e Interventistica Cardiologia, Viale Risorgimento, 80, 42100 Reggio Emilia, Italy	5/5
028	Dr Nick Ossei-Gerning/University Hospital of Wales, Heath Park, Cardiff, CF14 4XW, UK	2/2
029	Dr Matthias R. Schulze/Klinikum Schwalmstadt, Schwalm-Eder-Kliniken GmbH, Krankenhausstrasse 27, 34613 Schwalmstadt, Germany	18/18
030	Prof Forster Tamás/Szegedi Orvostudományi Egyetem, Kardiológiai Centrum, Korányi fasor 6, 6720 Szeged, Hungary	6/5
031	Dr Lupkovics Géza/Zala Megyei Kórház, Kardiológiai Osztály, Zrínyi Miklós u. 1, 8900 Zalaegerszeg, Hungary	7/7
032	Dr Apró Dezső/Állami Szívkórház Balatonfüred, 1. sz. Kardiológiai Osztály, Gyógy tér 2, 8230 Balatonfüred, Hungary	10/10
033	Prof. Tomasz Pasierski/Miedzyleski Szpital Specjalistyczny, Oddzial	14/14

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Appendix A (continued)		
Center no.	Investigator/affiliation	No. of subjects enrolled*/given CM
034	Kardiologii, Ul. Bursztynowa 2, 04-749 Warszawa, Poland Prof Sławomir Dobrzycki/ Samodzielny Publiczny Szpital Kliniczny AM w Białymstoku, Zakład Kardiologii Inwazyjnej, Ul. M. Skłodowskiej-Curie 24A, 15-276 Białystok, Poland	16/15
035	Prof. Waldemar Banasiak/4 Wojskowy Szpital Kliniczny, Ośrodek Chorób Serca, Ul. Weigla 5, 53-114 Wrocław, Poland	12/12
101	Warren Laskey, MD [†] /The University of New Mexico Health Science Center School of Medicine, Department of Internal Medicine MSC10-5550, 1 University of New Mexico, Albuquerque, NM 87131, USA D Michelle Ratliff, MD/Albuquerque Veterans Affairs Medical Center, 1501 San Pedro SE, Albuquerque, NM 87108, USA	19/17
102	Charles J. Davidson, MD/251 East Huron Street, Feinberg 8-256, Chicago, IL 60611, USA	26/26
103	Michael Rudnick, MD/Renal Electrolyte and Hypertension Division, Penn Presbyterian Medical Center, 240 Medical Office Building, 39th and Market St, Philadelphia, PA 19104, USA	9/9
104	Reda Ibrahim, MD/Montreal Heart Institute, 5000 East Belanger Street, Roulotte 1000A, Montréal, Québec, H1T 1C8, Canada	13/13
105	Center did not participate	–
106	Steven Rohrbeck, MD/Carolina Cardiology Associates, 306 Westwood Ave, Ste 401, High Point, NC 27262, USA	13/13
107	J. Lawrence Stafford, MD/University of Maryland Medical Center, 22 S Greene St, Room S3B08, Baltimore, MD 21201, USA	11/10
108	Edward O. McFalls, MD/Minneapolis Veterans Affairs Medical Center, One Veterans Dr, Cardiology 111C, Minneapolis, MN 55417, USA	13/13
109	Kendrick Shunk, MD/San Francisco Veterans Affairs Medical Center, 4150 Clement St, Mail Stop 151 CRC, San Francisco, CA 94121, USA	3/3
110	Frederick Weiland, MD/Sutter Roseville Medical Center, One Medical Plaza, Roseville, CA 95661, USA	0/0
111	Gary Schaer, MD/Rush University Medical Center, 1653 W Congress Pkwy, Ste 1035 Jelke, Chicago, IL 60612, USA	12/11
112	J. Huger Richardson, MD/South Carolina Heart Center, 2001 Laurel St, Columbia, SC 29204, USA	1/1

Appendix A (continued)		
Center no.	Investigator/affiliation	No. of subjects enrolled*/given CM
113	Peter C. Nishan, MD/LeBauer Cardiovascular Research Foundation, 1126 N Church St, Ste 300, Greensboro, NC 27401, USA	7/7
114	Christian Bounds, MD/Delmarva Heart Research Foundation, Inc, 106 Milford St, Ste 605, Salisbury, MD 21804, USA	10/10
115	Maurice Buchbinder, MD/Foundation for Cardiovascular Medicine, 9834 Genesee Ave, Ste 310, La Jolla, CA 92037, USA	0/0
116	Jesse Goldman, MD/Temple University Hospital, Parkinson Pavilion 658, 3401 N Broad St, Philadelphia, PA 19140, USA	10/10
117	Anthony Fung, MD/The University of British Columbia, Vancouver Hospital (VCH), Interventional Cardiology Research, 9176-2775 Laurel St, Vancouver, BC V5Z 1M9, Canada	15/15
118	Center withdrawn	–
119	John Hirshfeld, MD/University of Pennsylvania Medical Center, 9.119 Founders Pavilion, 3400 Spruce Street, Philadelphia, PA 19104, USA	12/12
120	Joseph Moore, MD/Jacksonville Center for Clinical Research, 4085 University Blvd South, Ste 1, Jacksonville, FL 32216, USA	4/3
121	Steven Weisbord, MD, MSc/ University of Pittsburgh, 200 Lathrop St, Pittsburgh, PA 15213, USA	15/14
122	Steven Weisbord, MD, MSc/VA Pittsburgh Healthcare System, University Drive Division (111F-U), Room 7E 120, Pittsburgh, PA 15240, USA	1/1
123	Lee A. MacDonald, MD, South Denver Cardiology Associates, PC, 1000 Southpark Dr, Littleton, CO 80120, USA	4/4
124	Anjali Acharya, MD, Jacobi Medical Center, North Bronx Healthcare Network, 1400 Pelham Parkway South, 6E-23B, Bldg I, Box 10461, Bronx, NY 10461, USA	4/4
125	John Collieran, MD, The Heart & Vascular Institute of Florida, 6006 49th St North, Ste 200, St Petersburg, FL 33709, USA	1/1
201a	Dr V Seshiah/Dr V Seshiah Diabetes Care and Research Institute, 31/A, Ormes Road Kilpauk, Chennai-600 010, Tamil Nadu, India	0/0
202a	Dr Vijay Viswanathan/Diabetes Research Centre & Hospital For Diabetes, 4, West Mada Church Street, Royapuram, Chennai-600 013, Tamil Nadu, India	0/0

Appendix A (continued)

Center no.	Investigator/affiliation	No. of subjects enrolled*/given CM
203	Dr Shreenivas Kumar/CARE Hospital, Road #1, Banjara Hills, Hyderabad-500 034, Andhra Pradesh, India	46/46
204	Dr Parthap Kumar (MD, DM FIC)/Manipal Hospital, Airport Road, 98 Rustumbagh, Bangalore-560 017, India	18/18

Appendix A (continued)

Center no.	Investigator/affiliation	No. of subjects enrolled*/given CM
205	Dr Pramod Jaiswal/Institute of Cardiac Vascular Disease, R-30-C, Ambattur Industrial Estate Road, Chennai-600 101, Tamil Nadu, India	16/14

* Assigned a subject study number.

† Coordinating investigator, Europe and India.

‡ Coordinating investigator, North America.