

A Meta-Analysis of the Renal Safety of Isosmolar Iodixanol Compared With Low-Osmolar Contrast Media

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OBJECTIVES	We sought to compare the nephrotoxicity of isosmolar contrast medium (IOCM) iodixanol with low-osmolar contrast media (LOCM) and to identify predictors of contrast-induced nephropathy (CIN).
BACKGROUND	Contrast-induced nephropathy is a serious complication of diagnostic and interventional procedures.
METHODS	Pooled individual patient data (n = 2,727) from 16 double-blind, randomized, controlled trials in which patients received either intra-arterial IOCM iodixanol (n = 1,382) or LOCM (n = 1,345) were included. Patients were stratified according to chronic kidney disease (CKD), diabetes mellitus (DM), or both. Outcome measures were the maximum increase in serum creatinine (Cr) over baseline and the incidence of postprocedural CIN.
RESULTS	The maximum Cr increase within 3 days after contrast medium (CM) administration was significantly smaller in the iodixanol group compared with the LOCM group (0.06 mg/dl vs. 0.10 mg/dl, p < 0.001), particularly in patients with CKD (0.07 mg/dl vs. 0.16 mg/dl, p = 0.004) and CKD + DM (0.10 mg/dl vs. 0.33 mg/dl, p = 0.003). Contrast-induced nephropathy, defined as an increase in Cr \geq 0.50 mg/dl within 3 days after CM administration, occurred less frequently in the iodixanol group than in the LOCM group in all patients (1.4% vs. 3.5%, p < 0.001), in CKD patients (2.8% vs. 8.4%, p = 0.001), and in CKD + DM patients (3.5% vs. 15.5%, p = 0.003). Independent predictors of CIN included CKD, CKD + DM, and use of LOCM.
CONCLUSIONS	This meta-analysis of pooled data from 2,727 patients indicates that use of the IOCM iodixanol is associated with smaller rises in Cr and lower rates of CIN than LOCM, especially in patients with CKD or CKD + DM. (J Am Coll Cardiol 2006;48:692-9) © 2006 by the American College of Cardiology Foundation

Contrast-induced nephropathy (CIN) remains one of the most clinically important complications of the use of iodinated contrast medium (CM) (1). Contrast-induced nephropathy is associated with considerably increased morbidity, including the need for short- and/or long-term hemodialysis or renal transplantation (2). Most importantly, the development of CIN is independently associated with increases in both in-hospital and long-term mortality (2-5). Clinically, CIN manifests as an abrupt decline in renal function occurring within 3 days of administration of CM in the absence of an alternative etiology (6). It is generally characterized by an initial increase in serum creatinine (Cr) concentration of at least 0.5 mg/dl or by a relative increase of at least 25% from baseline (6). Most episodes of CIN are self-limiting and resolve within 10 days (6). However, there is evidence that

even small persistent increases in Cr level are associated with increased mortality (7,8).

Patient- and CM-related risk factors have been identified that contribute to the likelihood and extent of CIN (9). Although the risk of CIN is low in patients with well-preserved renal function (10), chronic kidney disease (CKD) increases the risk of CIN from the normal incidence of \leq 2% up to 12% to 27% (9). Diabetes mellitus (DM) is possibly an independent risk factor for CIN (9); however, patients with concomitant CKD and DM have an incidence of CIN as high as 50% (9,11). Characteristics of CM, such as osmolality, might also influence the risk of CIN. Contrast media can be categorized according to osmolality (e.g., high-osmolar CM [HOCM] approximately 2,000 mOsm/kg, low-osmolar CM [LOCM] 600 to 800 mOsm/kg, and isosmolar CM [IOCM] 290 mOsm/kg) (6,12). In general, the lower the osmolality of a CM is, the better its safety profile is (13). Although the chemical composition of CM (ionic vs. non-ionic, monomer vs. dimer) might also contribute to the pathogenesis of CIN (12,13), significant clinical differences between various LOCM have not been established (14-16). All LOCM are considered functionally identical in therapeutic guidelines issued by the European

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Abbreviations and Acronyms

CI	= confidence interval
CIN	= contrast-induced nephropathy
CKD	= chronic kidney disease
CM	= contrast media
Cr	= creatinine
DM	= diabetes mellitus
HOCM	= high-osmolar contrast media
IOCM	= isosmolar contrast media
LOCM	= low-osmolar contrast media

Society of Urogenital Radiology and the American College of Radiology (9,17).

There is growing evidence that the IOCM iodixanol reduces the risk of CIN in patient populations with CKD or CKD with DM when compared with the LOCM iohexol (18,19), but small comparative trials of iodixanol with LOCM in general patient populations have been equivocal (20-22). These studies generally have shown that there are no differences or only small, statistically insignificant differences in nephrotoxic effects between IOCM and LOCM, possibly because of insufficient statistical power (20-22). The aim of this meta-analysis was to pool patient-level Cr data from randomized, controlled trials and compare Cr changes after administration of iodixanol versus all types of LOCM in a large patient population with differing levels of risk for CIN, including a significant number of patients at high risk for renal complications.

METHODS

This meta-analysis included prospective, double-blind, randomized, controlled trials that compared iodixanol with LOCM in adult patients undergoing angiographic examinations and reported Cr values at baseline and after CM administration. The clinical trial data source for this meta-analysis was the iodixanol database owned by GE Healthcare (formerly Amersham Health; Waukesha, Wisconsin), representing data from all iodixanol angiographic clinical trials sponsored by Amersham Health in Europe or the United States between 1991 and 2003. Individual patient-level data from all trials satisfying the retrospective criteria for inclusion were pooled to create the database. Pooled data included demographic data (age, gender, weight), presence of DM, CM administered (kind, concentration, and volume), and Cr values at baseline and after administration.

Patient subgroups were formed after stratification by CKD and DM within the CM groups (IOCM vs. LOCM). The presence of CKD was determined by assessing baseline Cr concentration and estimated creatinine clearance (CrCl). All baseline Cr values were measured within 3 days before CM exposure. In 2,433 (89.2%) subjects, Cr was measured <24 h before CM administration. The CrCl was calculated by applying the Cockcroft-Gault formula to the baseline Cr concentration values:

$$\text{CrCl (ml/min)} = \left[\frac{(140 - \text{age})(\text{weight [kg]})}{72 \times \text{serum Cr (mg/dl)}} \right] (0.85 \text{ for women})$$

This equation closely correlates with measured CrCl (correlation coefficient 0.83) and assesses renal function more accurately than Cr alone (23). Patients were identified as having CKD if their baseline Cr concentrations were ≥ 1.50 mg/dl for men or ≥ 1.30 mg/dl for women or their CrCl was ≤ 60 ml/min.

Statistical analyses were performed on data pooled across trials. The primary outcome was the maximum increase in Cr within 3 days (baseline to highest value) after administration of contrast. Results are expressed as mean \pm standard deviation, and the differences between the CM groups were analyzed with the Student *t* test. Secondary outcomes were the incidence of CIN, defined as an increase in Cr concentration of ≥ 0.50 mg/dl or ≥ 1.00 mg/dl over baseline within 72 h after contrast administration. These proportions were compared with the Fisher exact test. For all tests, a *p* value < 0.05 was considered statistically significant. Quantitative analysis (meta-analysis) was conducted on these data by calculating odds ratios (ORs) and 95% confidence intervals (CIs) for each study. A chi-square test with *n*-1 degrees of freedom (df), where *n* is the number of tested trials, was used to test for heterogeneity. This heterogeneity analysis was used to guide the choice of effect model used for the analysis. Because there was no significant heterogeneity (*p* > 0.10) a fixed effects model was used. An overall OR with 95% CI was calculated, with studies weighted according to the Mantel-Haenszel method, with Review Manager 4.2.7 software.

Multivariate logistic-regression analysis was used to determine predictors of CIN. The response variable was the incidence of CIN defined as an increase in Cr concentration of ≥ 0.50 mg/dl. Odds ratios and their two-sided 95% CIs are reported, and significance was determined by the position of the 95% CIs. A CI not including 1 was considered statistically significant.

Role of the funding source. GE Healthcare sponsored the original studies, collected the data in collaboration with independent investigators, and provided site-monitoring and data management. Analyses were requested by the authors and performed by GE Healthcare statistical staff.

RESULTS

Sixteen trials fulfilled the criteria for inclusion in the meta-analysis (Table 1): 7 trials in coronary angiography or intervention (19,24-29), 5 trials in aortic or peripheral angiography (20,30-33), 1 trial in visceral and femoral angiography (34,35), 1 trial in cerebral angiography (36), 1 unpublished trial in angiography, and 1 unpublished trial in visceral/peripheral arteriography (Appendix).

From the total of 3,008 patients who were included in these trials, 281 (9.3%) were excluded from the meta-analysis for reasons including no or mixed CM administra-

Table 1. Characteristics of 16 Trials Included in Meta-Analysis (19,20,24-36)

Trial Diagnostic Procedure, Reference	No. of Patients Included in the Trial	No. of Patients Eligible for Inclusion in the Meta-Analysis	No. of Patients		Creatinine Measurements			
			IOCM Iodixanol	LOCM	Baseline	Day		
						1	2	3
Cardioangiography, Kløw et al. (27)	80	72	35	37	X	X	X	
Cardioangiography, Tveit et al. (29)	94	92	49	43*	X	X	X	
Cardioangiography, Andersen et al. (24)	76	74	36	38*	X	X	X	
Cardioangiography, Manninen et al. (28)	130	128	68	60	X	X		
Cardioangiography, data on file	50	49	25	24	X	X	X	
Cardioangiography, Aspelin et al. (19)	135	132	66	66	X		X X	
Cardioangiography, Hill et al. (26)	200	195	97	98	X	X	X X	
Femoral angiography, Pugh et al. (20)	100	93	47	46	X	X	X	
Femoral angiography, Thorstensen et al. (31)	74	65	34	31	X	X		
Aortoangiography, Singh et al. (30)	60	60	40	20	X	X		
Aortoangiography, Jakobsen et al. (33)	16	16	8	8	X	X	X X	
Femoral angiography, Verow et al. (32)	145	144	75	69	X	X		
Angiography (visceral and femoral), data on file	110	101	49	52	X		X X	
Angiography (visceral and femoral), Siegel et al. (35) + Rosenblum et al. (34)	100	97	49	48*	X	X	X X	
Cerebral angiography, Poirier et al. (36)	100	95	50	45	X	X	X X	
PTCA, Bertrand et al. (25)	1,541	1,314	654	660*	X	X	X	
Total	3,008	2,727	1,382	1,345				

*Indicates LOCM ionic dimer ioxaglate.

IOCM = isosmolar contrast media (iodixanol); LOCM = low-osmolar contrast media (non-ionic monomers [iohexol, iopromide, iopamidol] and ionic dimer ioxaglate); PTCA = percutaneous transluminal coronary angioplasty.

tion and missing Cr measurements. Thus, the meta-analysis was based on 2,727 evaluable patients: 1,382 (50.7%) in the iodixanol group and 1,345 (49.3%) in the LOCM group.

Pooled demographic and baseline characteristics of the patient population are summarized in Table 2. Treatment groups were comparable in terms of age and gender. The demographics of subgroups stratified on the basis of renal status, diabetes, or both conditions were also comparable. Patients given iodixanol and LOCM received comparable volumes of CM (mean difference 6.2 ml), with a slight but statistically significant decrease in the total iodine dose received by the iodixanol group compared with the LOCM

group, mainly owing to the lower iodine concentration of iodixanol.

Patients received different formulations of CM. The 1,382 iodixanol patients were given either the 270 mg I/ml or the 320 mg I/ml formulation. Patients receiving non-ionic, monomeric LOCM were given iohexol 300 mg I/ml or 350 mg I/ml (n = 381), iopamidol 300 mg I/ml (n = 69), or iopromide 300 mg I/ml or 370 mg I/ml (n = 106). The remainder of patients given LOCM were given the ionic dimer, ioxaglate 320 mg I/ml (n = 789).

Serum Cr measurements were available at baseline for all patients, but the timing of subsequent Cr measurements was

Table 2. Demographic Information

Variable	All Patients (n = 2,727)	Contrast Media		p Value
		IOCM Iodixanol (n = 1,382)	LOCM (n = 1,345)	
Age, yrs (mean ± SD)	61.5 ± 11.8	61.2 ± 11.9	61.8 ± 11.6	NS
Male gender	1,999	1,011	988	NS
CKD	735	362	373	NS
DM	568	293	275	NS
Mean baseline Cr (mg/dl)				
With CKD	1.47 ± 1.00	1.43 ± 0.89	1.50 ± 1.10	NS
Without CKD	1.00 ± 0.18	1.01 ± 0.18	1.00 ± 0.18	NS
CKD and DM	232	115	117	NS
Total volume (ml) (mean ± SD)	179.0 ± 94.6	175.9 ± 91.3	182.1 ± 97.8	0.09
Total dose (g iodine) (mean ± SD)	57.2 ± 30.1	55.4 ± 29.1	58.9 ± 31.0	0.003
Indication for CM				
Cardioangiography	2,072	1,038	1,034	NS
Arteriography	655	344	311	NS

CKD = chronic kidney disease; CM = contrast medium; DM = diabetes mellitus; IOCM = isosmolar contrast media; LOCM = low-osmolar contrast media.

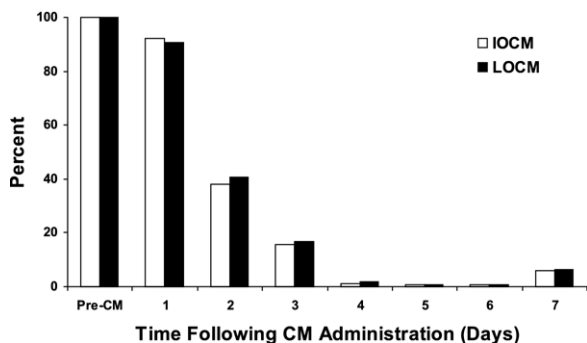


Figure 1. The proportion of patients with a creatinine measurement available on the days after administration of contrast media (CM). Patients received either isosmolar contrast media (IOCM) (iodixanol) or low-osmolar contrast media (LOCM). Pre-CM = baseline before contrast media was given.

variable with >99% of subjects with measurements within the first 48 h (Fig. 1). Only 18.3% of patients had their final Cr values measured on day 3 or later.

The overall population examined in this study was heterogeneous with respect to risk factors for and the incidence of CIN. However, greater homogeneity was found within patient subgroups defined on the basis of common risk factors (DM and CKD), which enabled comparison of increases in Cr and CIN incidence within these subgroups. Only two of the trials were designed to examine the renal safety of CM in patients with CKD (19,33).

The maximum measured increases in Cr from baseline after contrast administration in all patients and in patient subgroups up to day 3 are given in Figure 2. A comparison of all patients, regardless of risk factors, showed that the maximum increase in Cr was significantly less in patients treated with iodixanol than with LOCM (0.06 mg/dl vs. 0.10 mg/dl, $p < 0.001$). A similar result was obtained in the subgroups of patients with CKD (0.07 mg/dl vs. 0.16 mg/dl, $p = 0.004$) and without CKD (0.06 mg/dl vs. 0.08 mg/dl, $p = 0.01$). A significantly lesser change from baseline was also observed for patients with DM alone

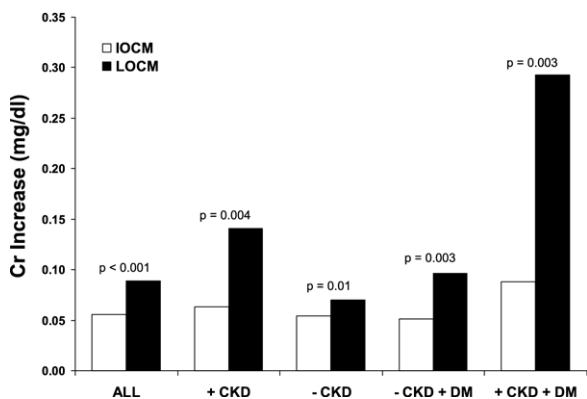


Figure 2. Maximal absolute increase in the creatinine (Cr) concentration from baseline to day 3, after contrast administration. The differences in Cr between the IOCM iodixanol and LOCM groups were compared with the Student *t* test. Patients received either IOCM or LOCM. CKD = chronic kidney disease; DM = diabetes mellitus; other abbreviations as in Figure 1.

Table 3. Maximum Increase in Serum Cr After Contrast Exposure: Analysis by Chemical Composition and Trial Comparison

CM Composition	n	Maximum Cr Increase (mg/dl)	p Value
Non-ionic, dimeric IOCM (iodixanol)	594	0.12 ± 0.16	
Non-ionic, monomeric LOCM (iohexol, iopromide, iopamidol)	552	0.18 ± 0.43	0.001
Non-ionic, dimeric IOCM (iodixanol)	788	0.02 ± 0.16	
Ionic, dimeric LOCM (ioxaglate)	788	0.05 ± 0.21	0.01

From baseline to day 3.

CM = contrast media; Cr = creatinine; IOCM = isosmolar contrast media; LOCM = low-osmolar contrast media.

treated with iodixanol compared with LOCM (0.06 mg/dl vs. 0.11 mg/dl, $p = 0.003$). Finally, in high-risk patients with CKD + DM, the maximal Cr increase was significantly smaller in the iodixanol group compared with the LOCM group (0.10 mg/dl vs. 0.33 mg/dl, $p = 0.003$). Table 3 shows that the maximum serum Cr rise was lower with iodixanol versus non-ionic or ionic LOCM.

The incidence of CIN (Cr ≥0.50 mg/dl) occurring within 72 h after contrast administration among the iodixanol- and LOCM-treated groups is summarized in Table 4. The incidence of CIN was also lower in patients given iodixanol than in those given *non-ionic monomeric* LOCM (2.4% vs. 6.2%, OR = 0.37, 95% CI 0.20 to 0.69, $p = 0.002$). This difference was amplified in patients with CKD (5.1% vs. 13.3%, OR = 0.35, 95% CI 0.16 to 0.79, $p = 0.01$). A similar trend was observed in patients given iodixanol rather than *ionic dimeric* LOCM (0.6% vs. 1.6%, OR = 0.38, 95% CI 0.14 to 1.07, $p = 0.09$), with a greater difference in patients with CKD (0.5% vs. 4.4%, OR = 0.12, 95% CI 0.01 to 0.94, $p = 0.02$).

The incidence of CIN in the pooled population, with the more stringent definition for increase in Cr of ≥1.00 mg/dl, was 0.1% in the iodixanol group and 1.2% in the LOCM group (OR = 0.06, 95% CI 0.01 to 0.45, $p < 0.001$). The incidence of CIN was also significantly lower among patients treated with iodixanol than with LOCM in patient subgroups with CKD (0.3% vs. 3.8%, OR = 0.07, 95% CI 0.01 to 0.54, $p = 0.001$) and CKD + DM (0% vs. 7.8%, $p = 0.003$).

A chi-square test ($df = 9$) for heterogeneity applied for trials in which at least one subject experienced CIN (10 of 16) was not significant ($p = 0.25$), indicating homogenous incidence rates for CIN among these trials (Fig. 3). According to this result, the fixed effects model was used to test the overall effect. The test for the overall effect showed a significant difference in favor of iodixanol (overall OR = 0.39, 95% CI 0.23 to 0.66, $p = 0.0004$). Given the strong influence of the trial by Aspelin et al. (19)—which had the lowest OR, a modest sample size, and highest weight—the meta-analysis was re-run without including this trial. Again, the test for heterogeneity was not significant ($p = 0.52$) and the fixed effects test for the overall effect showed a signifi-

Table 4. Rates of Contrast-Induced Nephropathy Defined as a Rise in Cr ≥ 0.5 mg/dl: Analysis by Patient Subgroup

Population	Number of Patients IOCM Iodixanol/LOCM	IOCM Iodixanol n (%)	LOCM n (%)	OR (95% CI)	Fisher Exact Test p Value
All	1,382/1,340*	19 (1.4)	47 (3.5)	0.38 (0.22-0.66)	<0.001
+CKD	362/371	10 (2.8)	31 (8.4)	0.31 (0.15-0.65)	0.001
-CKD	1,020/969	9 (0.9)	16 (1.7)	0.53 (0.23-1.21)	0.16
+CKD + DM	115/116	4 (3.5)	18 (15.5)	0.20 (0.06-0.60)	0.003
+CKD - DM	247/255	6 (2.4)	13 (5.1)	0.46 (0.17-1.24)	0.16
-CKD + DM	178/158	1 (0.6)	3 (1.9)	0.29 (0.03-2.84)	0.35
-CKD - DM	842/811	8 (1.0)	13 (1.6)	0.59 (0.24-1.43)	0.28

*Five patients without follow-up Cr value within 3 days.

CI = confidence interval; CKD = chronic kidney disease; Cr = serum creatinine; DM = diabetes mellitus; IOCM = isosmolar contrast media; LOCM = low-osmolar contrast media; OR = odds ratio.

cant difference in favor of iodixanol (overall OR = 0.55, 95% CI 0.30 to 0.99).

Independent predictors of CIN (Cr ≥ 0.50 mg/dl) identified through logistic regression analysis were: CKD (OR = 3.1, 95% CI 1.7 to 5.6), combination of CKD + DM (OR = 2.7, 95% CI 1.4 to 5.1), and the use of LOCM (OR = 2.6, 95% CI 1.5 to 4.5). Age, DM alone, and CM volume were found not to be independent predictors of CIN in the model.

DISCUSSION

This meta-analysis was performed with pooled individual data of patients given iodixanol (n = 1,382) or a LOCM (n = 1,345) intra-arterially for a variety of diagnostic and interventional procedures. In all patients, the increase in Cr associated with administration of CM was smaller in patients given iodixanol than in the pooled LOCM population. The lesser increase in Cr observed with iodixanol was associated with a reduced incidence of CIN according to both standard (≥ 0.50 mg/dl) and stringent (≥ 1.00 mg/dl) definitions. The largest absolute difference in the incidence

of CIN found between patients given iodixanol and those given LOCM was in subgroups with CKD or CKD + DM. Patient-related predictors of CIN were found to be CKD and CKD + DM but not DM alone. Use of LOCM was a procedure-related predictor of increased CIN risk. The volumes of contrast in the two groups were similar (approximately 180 ml) and in the range where CIN has been found to be a serious complication in patients undergoing cardiovascular procedures (3,37). These data are internally consistent with the hypothesis that iodixanol (290 mOsm/kg) is less nephrotoxic than LOCM agents with osmolalities ranging from 600 to 800 mOsm/kg in the volumes of contrast used in these trials.

Previous studies of nephrotoxicity. Previous clinical trials have demonstrated that as osmolality is reduced, lesser rates of CIN are observed (38,39). In a prospective, randomized trial involving 1,196 patients, 213 patients had CKD + DM (38). The incidence of CIN (Cr ≥ 0.50 mg/dl) in this high-risk population was 33.3% in the LOCM group and 47.7% in the HOCM group. No differences were found between the two types of CM in patients with normal renal

Outcome: Contrast Induced Nephropathy (CIN), defined as Cr increase ≥ 0.5 mg/dl

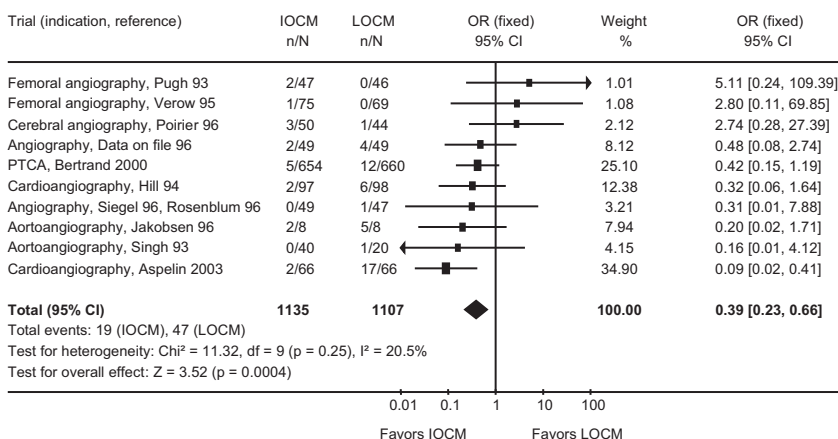


Figure 3. Summary of all trials in which at least 1 subject experienced contrast-induced nephropathy (CIN) defined as a rise in Cr ≥ 0.50 mg/dl (10 of 16). The chi-square test for heterogeneity was not significant (p = 0.25), indicating homogenous incidence rates for CIN among these trials. According to this result, the fixed effects model was chosen to test the overall effect. The test for the overall effect showed a significant difference in favor of the group receiving IOCM, with the odds ratio (OR) = 0.39, 95% confidence interval (CI) 0.23 to 0.66, p = 0.0004 (19,20,25,26,30,32-36). Heterogeneity test for trials in which at least 1 patient experienced CIN (10 of 16), and test for the overall effect with trials weighted according to the Mantel-Haenszel method, with the Review Manager 4.2.7. n = number of patients who experienced CIN defined as Cr increase ≥ 0.50 mg/dl; N = number of patients with Cr measurements; PTCA = percutaneous transluminal coronary angioplasty (trial [25]); other abbreviations as in Figure 1.

function, regardless of the presence of DM. Similarly, the present meta-analysis showed that reducing osmolality the next level from LOCM to IOCM reduced the incidence of CIN in patients with CKD but did not reduce the incidence of CIN in patients without CKD.

A smaller meta-analysis ($n = 697$) previously compared the nephrotoxicity of the IOCM iotrolan (280 mg I/dl) with LOCM, including iopamidol (300 mg I/dl), iopromide (300 mg I/dl), and iohexol (300 mg I/dl) in a general population (39). Consistent with the present meta-analysis of iodixanol, the increase in Cr at 48 h was significantly smaller after iotrolan than LOCM in all patients as well as in patients with CKD. This study offers further support for the notion that IOCM agents have the lowest degree of nephrotoxicity.

Our findings are consistent with those from a small head-to-head comparison of iodixanol and iohexol in patients with CKD that is not part of the iodixanol database owned by GE Healthcare (18). In that study, 102 patients with pre-existing CKD ($Cr >1.5\text{mg/dl}$) were randomized to iodixanol 320 mg I/dl or 270 mg I/dl ($n = 54$) or iohexol 300 mg I/dl ($n = 48$) (18). With CIN defined as an increase of $>25\%$ in Cr concentration from baseline, the incidence of CIN was 3.7% and 10.0% in the iodixanol and iohexol groups, respectively. Because of the small sample size, the difference was not statistically significant. Nevertheless, these data compare favorably with the statistically significant results of the current study, in which the incidence of CIN ($Cr \geq 0.50\text{mg/dl}$) in patients with CKD was 2.8% with iodixanol and 8.4% with LOCM ($p = 0.001$).

A recently presented percutaneous coronary intervention (PCI) registry involving 7,769 patients compared 3 years' data with LOCM (iohexol; $n = 5,855$), followed in the next year with IOCM (iodixanol; $n = 1,914$) (40). Baseline demographics were similar in those who received iohexol and iodixanol, however, Cr was higher in the iohexol period, (1.18 ± 0.01 [mean \pm SD] vs. 1.12 ± 0.02 , $p < 0.05$). There were significantly more patients with DM (26% vs. 29%, $p < 0.01$) and hypertension (58% vs. 65%, $p < 0.01$) in the group receiving iodixanol. The prevalence of CIN, defined as a rise in Cr $>25\%$ within 24 h after PCI, was 7.57% with iohexol and 5.26% with iodixanol (30.5% relative reduction, $p < 0.01$). The authors concluded that iodixanol use in a general population of patients is associated with reduced risk for CIN, consistent with this meta-analysis.

Predictors of contrast-induced nephropathy. Patient-related risk factors for CIN have previously been established to include chronic CKD and DM (41). The incidence of LOCM-related CIN in diabetic patients with CKD has ranged from 5.7% to 29.4% in prior studies (41,42). Our reported rate of CIN (15.5%) is well within this range. Furthermore, this meta-analysis confirms the primary importance of CKD and CKD + DM as risk factors for CIN. Use of LOCM was found to be an independent procedural predictor of CIN, but volume of CM was not. The latter

results seem consistent with a retrospective analysis demonstrating no significant correlation between iodixanol volume and Cr increase in patients with CKD (43).

Contrast osmolality and renal injury. Contrast media is classified according to osmolality, which reflects the total particle concentration of the solution (the number of molecules dissolved in a specific volume). Over the past 40 years, the osmolalities of available CM have been gradually decreased to physiological levels. In the 1950s, only HO CM (e.g., diatrizoate) with osmolality 5 to 8 times that of plasma were available (44). In the 1980s, LOCM agents such as iohexol, iopamidol, and ioxaglate were introduced. Although these are classified as LOCM, their osmolality is 2 to 3 times greater than that of plasma (44). In the 1990s, IOCM with the same physiologic osmolality as blood were developed (e.g., iodixanol) (44). Red blood cell deformation, systemic vasodilation, intrarenal vasoconstriction, as well as direct renal tubular toxicity are all more common in contrast agents with osmolality greater than that of blood (44).

Study strengths and limitations. A major strength of this study is the size and quality of the database used. All of the studies were randomized, prospective trials in which the treatment allocation was iodixanol versus LOCM. Analysis of the pooled, patient-level (as opposed to tabular) data permitted estimation of the difference in the incidence of nephrotoxicity between iodixanol and LOCM in all patients and in specific patient subgroups. It is important to note that despite variations in baseline risk, CM dose, timing of Cr measurements, and comparator LOCM, significant differences in CIN were consistently observed between iodixanol and LOCM agents. Meta-analyses that include studies where there is no randomization of CM and no patient-level data are unable to quantify baseline risk or perform subgroup analyses and, very importantly, might fail to find existing differences between specific CM.

An additional strength of our study was the inclusion of all trials (including 2 unpublished) in the database to avoid publication bias, which is a common threat to the validity of meta-analyses. Given that the 2 unpublished studies were small, underpowered, and neutral on CIN (iodixanol vs. LOCM), their exclusion from this analysis would bias results toward the hypothesis that iodixanol has greater renal safety than LOCM.

Operator bias is a potential threat to validity of any meta-analysis focusing on the reduction of a procedural complication. That is, the actions of operators performing contrast procedures with the aim of reducing CIN might influence the outcomes. This was handled by the use of patient-level data, multivariate analysis controlling for the volume of contrast used, and by restrictive protocols that did not allow the use of N-acetylcysteine or any other investigational prophylactic therapy (45). However, the operators might have influenced the outcomes in our trials in that the amount or type of intravenous hydration given before and after the contrast exposure was not recorded in our database.

Another limitation of this meta-analysis is that the early timing of the Cr measurements might have resulted in an underestimation of the incidence of CIN in both experimental groups. Although the maximum increase in Cr indicative of CIN is generally observed up to 3 days after administration of CM (6) or even 3 to 5 days after CM administration (46), the majority of Cr measurements were available only for day 1 or day 2, and some cases of CIN might have been missed. However, it is unlikely that serious cases of CIN were missed, because they are usually detected within the first 24 h after the contrast exposure (47).

Finally, outcome data on the longer-term consequences of exposure to iodixanol versus LOCM were not available. However, prior studies have demonstrated that even transient rises in Cr translate into differences in adjusted long-term outcomes after PCI (7,48). Mild sustained increases in Cr have been observed to increase the risk of death by 3-fold over 8 years (8). Thus, the impact of this study on clinical practice, with the anticipated sharp increase in iodinated contrast media with computed tomographic coronary angiography, is 2-fold: 1) the presence of CKD and DM should be known *a priori*, and 2) iodixanol should be considered in those with CKD and in particular those with CKD and DM.

Conclusions. The results of this meta-analysis indicate that intra-arterial administration of the IOCM iodixanol is associated with a reduced risk for CIN compared with LOCM. The reduction in the mean Cr increase and in the incidence of CIN is greatest in patients with CKD or CKD + DM. These results support the use of iodixanol to prevent contrast-related renal dysfunction in patients at risk for CIN.

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APPENDIX

For a description of the previously unpublished trials included in the meta-analysis, please see the online version of this article.