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Nephrotoxicity of Iso-osmolar Iodixanol Compared with Nonionic Low-osmolar Contrast Media: Meta-analysis of Randomized Controlled Trials[1]

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Purpose: To compare the nephrotoxicity of iso-osmolar iodixanol with that of nonionic low-osmolar contrast media (CM) (LOCM) in randomized clinical trials.

Materials and Methods: This meta-analysis was conducted with a systematic search of MEDLINE, EMBASE, BIOSIS, Web of Science, ISI Web of Knowledge, Current Contents Medizin, Cochrane Library (until August 2007), trial registers, conference proceedings, and reference lists to identify studies and with requests from all manufacturers of CM for unidentified studies. Randomized controlled trials assessing serum creatinine levels before and after intravascular application of iodixanol or LOCM were included. The primary outcome measures were the incidence of contrast medium–induced nephropathy (CIN) and change in serum creatinine levels.

Results: Twenty-five trials were included. Iodixanol did not significantly reduce the risk of CIN (relative risk [RR], 0.80; 95% confidence interval [CI]: 0.61, 1.04; weighted mean difference in serum creatinine increase, 0.01 mg/dL [0.88 μmol/L]; 95% CI: −0.01, 0.03). There was no significant risk reduction after intravenous administration of the CM (RR, 1.08; 95% CI: 0.62, 1.89); subgroup with preexisting renal insufficiency (RR, 1.07; 95% CI: 0.56, 2.02) or after intraarterial administration (RR, 0.68; 95% CI: 0.46, 1.01); subgroup with preexisting renal insufficiency (RR, 0.59; 95% CI: 0.33, 1.07). However, in patients with intraarterial administration and renal insufficiency, the risk of CIN was greater for iohexol than for iodixanol (RR, 0.38; 95% CI: 0.21, 0.68), whereas there was no difference between iodixanol and the other (noniohexol) LOCM (RR, 0.95; 95% CI: 0.50, 1.78).

Conclusion: Iodixanol is not associated with a significantly reduced risk of CIN compared with the LOCM pooled together. However, in patients with intraarterial administration and renal insufficiency, iodixanol is associated with a reduced risk of CIN compared with iohexol, whereas no significant difference between iodixanol and other LOCM could be found.

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Contrast medium–induced nephropathy (CIN) is regarded as one of the most important complications after intravascular administration of radiographic contrast media (CM) (Table 1) and as one of the most common causes of hospital-acquired acute renal failure (1). Because of the technical innovations in diagnostic imaging and catheter-based interventions, there are continued substantial increases in patient exposure to iodinated CM. In the last 2 decades, the number of computed tomographic (CT) examinations increased by 800%, and an increase of 390% in cardiac catheterization procedures has been reported (2). In addition, the prevalence of risk factors for CIN, such as chronic kidney disease and diabetes mellitus, is increasing in our ever-growing aging population. The development of CIN, especially after percutaneous coronary interventions, is associated with prolonged hospital stay and substantial increases in costs, morbidity, and in-hospital and long-term mortality, with an in-hospital mortality rate of up to 34% and up to 62% when renal failure requiring renal replacement therapy occurs (3,4). In light of the increasing use of CM, particularly in high-risk patients, and the very poor outcome for patients with CIN, there is an urgent need for effective strategies for the prevention of CIN. However, strategies to prevent CIN, such as hydration and the use of acetylcysteine provide only incomplete protection or are not applicable for emergency procedures (5–8).

Great enthusiasm for the use of iso-osmolar iodixanol was elicited by the Nephrotoxicity in High-Risk Patients Study of Iso-osmolar and Low-osmolar Non-Ionic Contrast Media published in 2003 (9), in which the researchers found the incidence of nephropathy to be significantly less with the iso-osmolar contrast medium, as compared with low-osmolar iohexol, in patients with moderate renal insufficiency and diabetes mellitus who underwent angiographic procedures. That study, as well as a recently published meta-analysis of data from a database of the manufacturer of iodixanol that included studies up until 2003, have had a strong effect on the recommendations of several guidelines that suggest that nephrotoxicity of iodixanol, compared with the class of low-osmolar CM (LOCM), is reduced (10,11). Until that study, a definite benefit of iodixanol over that of LOCM in terms of nephrotoxicity had not been shown, and subsequent angiography trials provided conflicting results, leaving the question open as to whether the nephrotoxicity of iodixanol is less than that of other available iodinated contrast agents (12,13). In addition, researchers in other studies found no significant difference between iodixanol and nonionic LOCM, and some even noted a trend toward increased nephrotoxic effects with iodixanol after intravenous administration, causing the situation to become even more controversial (14,15). Thus, the aim of our systematic review and meta-analysis was to compare the nephrotoxicity of iodixanol with that of nonionic LOCM in randomized clinical trials.

Advances in Knowledge

- There is no significant reduction in the relative risk (RR) of contrast medium–induced nephropathy (CIN) with the use of iodixanol, compared with nonionic low-osmolar contrast media (CM) (LOCM) pooled together.
- After intravenous contrast medium application, there is no benefit of iodixanol over the nonionic LOCM.
- After intraarterial CM administration, there were discordant study findings, which seem to be caused by differences in the potential nephrotoxicity among the nonionic LOCM.
- In patients with intraarterial CM application and renal insufficiency, iohexol is associated with a greater risk of CIN than is iodixanol.
- In contrast, there is no significant difference in the RR of CIN between iodixanol and the other nonionic LOCM in high-risk patients.

Implication for Patient Care

- Iodixanol or a nonionic LOCM other than iohexol may be used in patients at risk for CIN.

Materials and Methods

There was no funding source for this study. Four authors (M.C.H., L.H., V.M., and W.B.) declared no conflicts of interest. One author (M.U.) received consulting fees from Bracco Diagnostics. Bracco Altana Pharma/Bracco Imaging Deutschland, (Konstanz, Germany) Bayer Schering Pharma (Berlin, Germany), and Nycomed (Konstanz, Germany) and is or was involved in research funded by Bracco, Bracco Altana Pharma, GE Healthcare (Chalfont St Giles, England), Nycomed, and Bayer Schering Pharma. Two authors (M.C.H. and M.U.) had full control of the data. One author (L.H.) was responsible for the statistical analyses.

Data Sources and Search Strategy

We performed a systematic literature search of electronic databases, registers on the Internet, abstracts from major scientific meetings, and reference lists of all relevant studies and consulted experts and the manufacturers of CM (Appendix A) (16).

Study Selection

We performed a systematic literature search of MEDLINE (1950 through August

Published online
10.1148/radiol.2501080833

Radiology 2009; 250:68–86

Abbreviations:
CI = confidence interval
CIN = contrast medium–induced nephropathy
CM = contrast media
LOCM = low-osmolar CM
RR = relative risk

Author contributions:
Guarantors of integrity of entire study, M.C.H., M.U.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, M.C.H., V.M., M.U.; statistical analysis, L.H.; and manuscript editing, M.C.H., W.B., M.U.

See Materials and Methods for pertinent disclosures.

2007), EMBASE (1974 through August 2007), BIOSIS (1975 through August 2007), Web of Science, ISI Web of Knowledge, Citation Databases: Science Citation Index Expanded (1987 through August 2007), Current Contents Medizin (2007), and the Cochrane Library (2007).

We included studies irrespective of blinding when the following criteria were met: prospective, randomized, controlled trial in which serum creatinine levels were assessed before and 24–72 hours after contrast medium administration or the incidence of a decrease in renal function above a threshold level in patients who were randomized to receive either iso-osmolar iodixanol or one of the nonionic LOCM for diagnostic or therapeutic procedures with intravenous or intraarterial CM application. No restrictions were placed on abstracts, conference proceedings, or language. We excluded studies that were retrospective or nonrandomized or those in which patients were not randomized to receive the contrast agent used. The studies were reviewed independently by two researchers (M.C.H. and M.U., each with more than 10 years of experience in investigating CIN) to determine whether they met the eligibility criteria for inclusion. Discrepancies were resolved in consensus.

Data Extraction and Quality Assessment

Two investigators (M.C.H. and M.U.) extracted data from all primary studies that fulfilled the eligibility criteria with use of a standardized form. An increase in serum creatinine level of more than 25% was used as the primary definition for CIN (17). Furthermore, we used an increase in serum creatinine level of more than 0.5 mg/dL (44.2 μmol/L) as the definition for CIN. These two investigators independently evaluated the methodological quality of the included trials. To determine an overall quality score, the validated five-point scale in the study by Jadad et al (18), which was also included in our statistical analysis, was used. Before performing the analysis, we proposed hypotheses for subgroup analysis (preexisting renal impairment [19], iohexol vs other nonionic LOCM [20,21], and intraarterial CM application in patients with chronic renal insufficiency [19]). More details are provided in Appendix B.

Data Synthesis and Analysis

The baseline characteristics were compared with the Wilcoxon rank sum test. Meta-analysis was performed to obtain pooled relative risks (RRs), pooled differences in serum creatinine level increase (weighted mean differences), and associated 95% confidence intervals (CIs) (22). Statistical heterogeneity of trial results was tested (23). Analyses were also performed *(a)* after exclusion of studies for which no data for the particular definition of CIN were available, *(b)* after exclusion of studies that were not published as a full-text article (abstracts), and *(c)* after weighting of the studies with a quality weight (24). We performed subgroup analyses, meta-regression analyses, and one-way and two-way analyses of variance (25). We examined the data for potential publication bias (26,27). The standard deviations for two studies were estimated according to the method of imputing standard deviations for changes from baseline (28). More details are provided in Appendix C.

Results

Data Analysis

Of the 926 publications we identified, 845 were rejected after a preliminary review because they were not original, they were not relevant to our aim, or they were duplicate reports. Of the 81 remaining studies suitable for assessment, 22 were excluded because serum creatinine levels were not measured before and 24–72 hours after contrast medium application, 13 were excluded because ionic ioxaglate was used, 10 were excluded because they were not randomized studies, and eight were excluded because they were review articles. Three further studies were excluded because no renal outcome measures were available despite that serum creatinine levels were measured before and 24–72 hours after contrast medium application (29–31). Thus, 25 randomized controlled trials that included 3270 patients were included in our meta-analysis (Fig 1) (9,12,14,15,32–54).

The outcome measure of CIN, defined as an absolute or relative increase of serum creatinine level above a threshold level, was available from 18 studies that included 2654 patients. The increase in serum creatinine level was

Table 1

Classification of Iodinated CM

CM Class	CM*	Osmolality (mOsm/kg H_2O)†
Ionic		
High osmolar	Diatrizoate (Renografin; Bracco Diagnostics, Princeton, NJ), iothalamate (Conray; Mallinckrodt, St Louis, Mo), and ioxitalamate (Telebrix; Guerbet, Roissy, France)	1500–1860
Low osmolar	Ioxaglate (Hexabrix; Mallinckrodt, St Louis, Mo)	Approximately 600
Nonionic		
Low osmolar	Iobitridol (Xenetix; Guerbet), iohexol (Omnipaque; GE Healthcare, Princeton, NJ), iomeprol (Iomeron; Bracco Diagnostics), iopamidol (Isovue, Solutrast; Bracco Diagnostics), iopromide (Ultravist; Bayer Vital, Leverkusen, Germany), and ioversol (Optiray; Mallinckrodt, Hazelwood, Mo)	521–695
Iso-osmolar	Iodixanol (Visipaque; GE Healthcare, Princeton, NJ), iotrolan (Isovist; Bayer Vital)	290–320

* Trade names and manufacturers' names with their locations are in parentheses.

† With a concentration of 300–320 mg of iodine per milliliter.

available from 22 studies that included 2850 patients (for six studies, additional data in regard to the increase in serum creatinine level from the publication of Grynne et al [55] were used). Eight trials investigated the intravenous administration of the contrast agents; 17 trials included patients with intraarterial administration. The mean dose of the CM ranged from 16 to 125 g of iodine. There were 11 studies in which iohexol was used, six studies in which iopamidol was used, four studies in which iopromide was used, two studies in which iomeprol was used, one study in which ioversol was used, and one study in which iobitridol was used. One thousand seven hundred and one patients were randomized to receive iodixanol and 1569 patients received nonionic LOCM (494 [31.5%], iohexol; 1075 [68.5%], a contrast agent other than iohexol). The mean age of the patients ranged from 52 to 73 years, the percentage of patients with diabetes mellitus varied between 0% and 100%, and the percentage of women ranged from 7% to 57%. In 11 studies that included 1653 patients, patients with chronic kidney disease with mean baseline serum creatinine values varying between 1.42 mg/dL (125.5 μmol/L) and 7.80 mg/dL (689.5 μmol/L) were examined exclusively. There were no significant differences in the baseline characteristics according to the Wilcoxon rank sum test: number of patients (P = .62), age (P = .58), percentage of female patients (P = .93), percentage of diabetic patients (P = .74), baseline serum creatinine concentration (P = .78), and contrast medium dose (P = .39). Details of the baseline characteristics and the trial characteristics are given in Tables 2 and 3, respectively. The median score used in the study by Jadad et al (18) was 3.5. Details of the study quality characteristics are presented in Table 4.

In five studies, investigators described significant differences in the incidence of CIN or in the increase in serum creatinine level between patients who received iodixanol and those who received nonionic LOCM: In two studies that included 562 patients, researchers found a significant difference in favor of the low-osmolar iomeprol and iopamidol (12,14). Investigators in three studies that included 458 patients found a significant difference in favor of iodixanol (9,36,38). The outcome variables are given in Table 5.

Pooling of All LOCM

The overall RR of CIN was not significantly decreased with iodixanol compared with all LOCM pooled together (RR, 0.80; 95% CI: 0.61, 1.04; P = .1) (Fig 2) by using an increase of at least 25% in serum creatinine level as the definition for CIN. There was no evidence for significant heterogeneity of trial results (Cochran Q test = 13.7, I^2 = 0%, P = .55). The overall RR of CIN was also not significantly decreased (RR, 0.75; 95% CI: 0.44, 1.26; P = .27) (Fig 3) when an increase of at least 0.5 mg/dL (44.2 μmol/L) in serum creatinine level as the definition for CIN was used. By using this definition for CIN, there was evidence of significant statistical heterogeneity of trial results (Cochran Q test = 26.8, I^2 = 44%, P = .03). There was also no significant difference between iodixanol and the LOCM in the increase in serum creatinine level, with a weighted mean difference of 0.01 mg/dL (0.88 μmol/L) (95% CI: −0.01, 0.03; P = .39). The results remained robust after exclusion of the two studies for which the standard deviations were estimated (0.01 mg/dL [0.88 μmol/L]; 95% CI: −0.01, 0.03; P = .36). There was evidence of significant heterogeneity of trial results by using the increase in serum creatinine level as the end point (Cochran Q test = 39.3, I^2 = 54%, P < .01).

The lack of a significantly reduced RR remained robust to sensitivity analyses in a fixed-effects model (RR, 0.79; 95% CI: 0.61, 1.01; P = .07) after exclusion of studies for which no data for CIN defined as an increase in serum creatinine level of 25% or more (36,38,41,42,51) were available (RR, 0.86; 95% CI: 0.63, 1.16; P = .33), after exclusion of studies that were not available as full-text articles in a peer-reviewed journal (32,36,38,39) (RR, 0.87; 95% CI: 0.64, 1.17; P = .34), and after weighting of the studies with the quality score of Jadad et al (18) (RR, 0.84; 95% CI: 0.62, 1.14; P = .26). There was no evidence to suggest publication bias according to the Begg funnel plot, as well as to the Begg (P = .82) and Egger (P = .72) tests.

Meta-regression Analysis

By using meta-regression analysis, baseline serum creatinine level (P = .24), age (P = .52), percentage of female patients (P = .24), contrast medium dose (P = .76), percentage of diabetic patients (P = .08), application route (P =

Figure 1

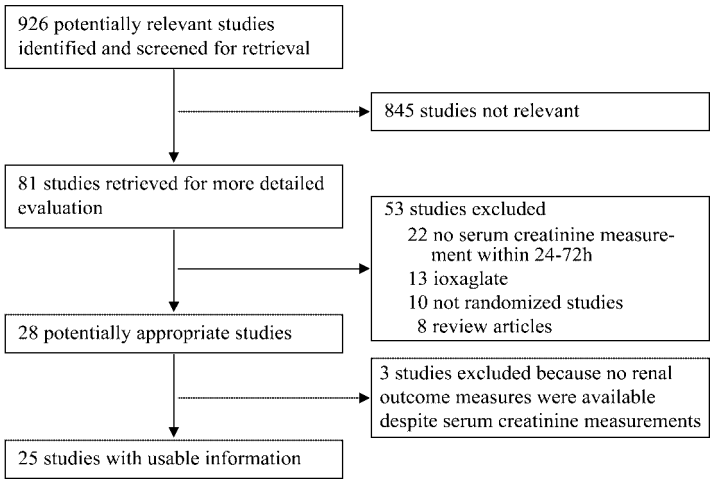


Figure 1: Study selection.

Table 2

Baseline Characteristics

Study and Year*	Sample Size	Age (y)		Women (%)†		Diabetic Patients (%)†		Baseline Serum Creatinine Level (mg/dL)‡		Dose§	
		Iodixanol	LOCM	Iodixanol	LOCM	Iodixanol	LOCM	Iodixanol	LOCM	Iodixanol	LOCM
Kuhn et al, 2008 (32)	248	68.3 ± 9.2	69.5 ± 10.1	50 (61/123)	57 (71/125)	100 (123/123)	100 (125/125)	1.41 ± 0.38	1.46 ± 0.44	32.5 ± 7.6	39.4 ± 9.4
Thomsen et al, 2008 (14)	148	65.4 ± 12.1	67.1 ± 14.1	36 (26/72)	24 (18/76)	12 (9/72)	28 (21/76)	1.7 ± 0.7	1.7 ± 0.6	40.0 ± 0	40.0 ± 0
Hardiek et al, 2008 (33)	102	65 ± 10	66 ± 10	52 (28/54)	33 (16/48)	100 (54/54)	100 (48/48)	0.91 ± 0.22	0.93 ± 0.24	46 ± 20	56 ± 30
Solomon et al, 2007 (12)	414	70.5 ± 9.9	72.4 ± 9.0	40 (83/210)	32 (66/204)	44 (92/210)	38 (78/204)	1.44 ± 0.41	1.46 ± 0.36	43.6 ± 22.9	49.5 ± 27.5
Schmid et al, 2007 (34)	114‖	60.6 ± 11.3	61.1 ± 9.9	31 (18/58)	27 (15/56)	22 (13/58)‖	12 (7/56)§	0.81 ± 0.20‖	0.83 ± 0.19‖	44.8 ± 15.04‖	51.1 ± 19.25‖
Feldkamp et al, 2006 (35)	221	60.6 ± 10.0	62.1 ± 9.2	25 (26/105)	24 (28/116)	40 (42/105)	35 (41/116)	1.04 ± 0.18	1.03 ± 0.19	124.5 ± 65.9‖	117.6 ± 69.2‖
Barrett et al, 2006 (15)	153	67.0 ± 11.5	67.3 ± 13.0	33 (25/76)	30 (23/77)	28 (21/76)	19 (15/77)	1.5 ± 0.5	1.6 ± 0.4	40.0 ± 1.3	40.4 ± 2.5
Rudnick, 2005 (36); Solomon and Rudnick, 2007 (37)	259	71.0	72.8	. . .	. . .	53 (71/134)	51 (64/125)	2.03	1.92	115.4 mL	130.0 mL
Sinha et al, 2004 (38)	70	70 ± 9	72 ± 6	. . .	. . .	40 (14/35)	34 (12/35)	2.04 ± 0.51#		. . .	. . .
Kolehmainen and Soiva, 2003 (39)	50	73.8 ± 12.7‖	72.0 ± 12.0‖	44 (11/25)‖	44 (11/25)‖	. . .	. . .	2.60 ± 1.59	2.74 ± 2.18	33.9 ± 0.9	36.1 ± 4.0
Aspelin et al, 2003 (9)	129	71.1 ± 6.0	70.6 ± 8.6	36 (23/64)	46 (30/65)	100 (64/64)	100 (65/65)	1.49 ± 0.53	1.60 ± 0.52	52 ± 28	57 ± 29
Chalmers and Jackson, 1999 (40)	102	62 (55, 70)**	65 (53, 69)**	28 (15/54)	31 (15/48)	31 (17/54)	35 (17/48)	3.05 (2.27, 4.42)**	3.34 (2.39, 5.48)**	17 (12, 30)**	16 (12, 31)**
Carraro et al, 1998 (41)	64	67 ± 14	69 ± 11	12 (4/32)	16 (5/32)	6 (2/32)	3 (1/32)	1.70 ± 0.29	1.69 ± 0.20	47.36 ± 6.82	45.84 ± 7.32
Siegle and Gavant, 1996 (42)	150	55 ± 17	52 ± 17	18 (18/100)	22 (11/50)	. . .	. . .	. . .	. . .	23.4 ± 4.9	24 ± 4.2
Lee et al, 1996 (43)	126	54 ± 15	54 ± 17	44 (38/87)	46 (18/39)	. . .	. . .	1.01 ± 0.24	1.08 ± 0.42	34.4 ± 8.7	35.7 ± 7.9
Jakobsen et al, 1996 (44)	16	55	58	12 (1/8)	38 (3/8)	0	0	6.3 ± 1.50	7.8 ± 2.27	27.84	27.65
Fischbach et al, 1996 (45)	39††	61.9 ± 10.7	60.2 ± 10.5	23 (14/60)	23 (13/57)	. . .	. . .	1.0 ± 0.15	1.1 ± 0.35	58.43 ± 18.14	74.22 ± 16.72
Manninen et al, 1995 (46)	119	55.1 ± 7.4	53.3 ± 9.1	22 (13/59)	18 (11/60)	. . .	. . .	. . .	. . .	38.9 ± 4.32	46.5 ± 6.25
Verow et al, 1995 (47)	134	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	25.8 ± 11.8	26.1 ± 14.4
Flinck et al, 2000 (48); Flinck et al, 1994 (49)	119	62.4 ± 9.5‖	63.0 ± 8.5‖	19 (11/59)	7 (4/60)	2 (1/59)‖	7 (4/60)‖	1.21 ± 0.17‖	1.21 ± 0.14‖	33.6 ± 6.7	35.3 ± 7.1
Thorstensen et al, 1994 (50)	67‡‡	67.6 ± 12.5	67.8 ± 11.3	42 (31/73)	45 (33/74)	. . .	. . .	0.93 ± 0.23	0.98 ± 0.26	61.7 ± 12.8	68.4 ± 15.6
Hill et al, 1994 (51)	200	61 ± 10	59 ± 11	20 (20/101)	12 (12/99)	. . .	. . .	. . .	. . .	32.96 ± 14.72	36.05 ± 12.95
Singh et al, 1993 (52)	59	59	66	26 (10/39)	40 (8/20)	. . .	. . .	0.91 ± 0.26	0.92 ± 0.27	63.7	76.4
Pugh et al, 1993 (53)	95	65.0 ± 8.9	68.0 ± 10.4	26 (12/48)	28 (13/47)	. . .	. . .	1.14	1.14	. . .	. . .
Klow et al, 1993 (54)	72	54 ± 9	55 ± 9	. . .	. . .	. . .	. . .	. . .	. . .	56 ± 4.8	60.9 ± 5.25

Note.—Data are the means or the means ± standard deviations, except where otherwise indicated.

* Reference 36 was not a full-text article, and references 38, 39, and 49 were published as abstracts only.

† Numbers in parentheses were used to calculate the percentages.

‡ To convert values for serum creatinine to Système International units (micromoles per liter), multiply by 88.4.

§ Values are in grams of iodine unless otherwise indicated.

‖ Data were missing in the original publication.

This value is the mean for iodixanol and LOCM groups pooled together.

** Data are the medians, and numbers in parentheses are the 1st and 3rd quartiles, respectively.

†† Serum creatinine measurements were performed in 39 of 117 patients.

‡‡ Serum creatinine measurements were performed in 67 of 147 patients.

Table 3

Trial Characteristics

Study and Year*	LOCM	Only Renal Insufficiency Patients Included†	Application Route	Procedure‡	Hydration§	Preventive Drugs‖
Kuhn et al, 2008 (32)	Iopamidol	Yes; estimated glomerular filtration rate, 20–59 mL/min/1.73 m^2	Intravenous	CT	Not standardized; hydration performed—iodixanol, 7.3%; LOCM, 8.8%, P = .82; intravenous volume—iodixanol, 928 mL ± 803; LOCM, 833 mL ± 740, P = .78	ACC allowed; iodixanol, 1.6%; LOCM, 2.4%; P => .99
Thomsen et al, 2008 (14)	Iomeprol	Yes; ≥1.5 mg/dL serum creatinine level and/or 10–59 mL/min/1.73 m^2 creatinine clearance	Intravenous	CT	Not standardized; hydration performed—iodixanol, 11.1%; LOCM, 13.2%, P = .70; intravenous volume—iodixanol, 1369 mL ± 1070; LOCM, 1125 mL ± 358, P = .55	No preventive drug treatment
Hardiek et al, 2008 (33)	Iopamidol	No; serum creatinine level, ≤2 mg/dL	Intraarterial	Diagnostic or interventional angiography; 99% coronary, 19% renal, 8% carotid, 4% peripheral arteries	Not standardized; intravenous fluids, 1 mL/kg/h, from arrival until discharge	No ACC or theophylline
Solomon et al, 2007 (12)	Iopamidol	Yes; estimated glomerular filtration rate, 20–59 mL/min/1.73 m^2	Intraarterial	Diagnostic cardiac angiography; percutaneous coronary intervention—iodixanol, 39.0%; LOCM, 39.7%	Standardized; isotonic sodium bicarbonate, 3 mL/kg/h 1 h before and 1 mL/kg/h during and 6 h after procedure	ACC, 1200 mg orally twice per day for 2 days, allowed; iodixanol, 42.4%; LOCM, 38.7%; P = .48
Schmid et al, 2007 (34)	Iomeprol	No; serum creatinine level, ≤2.5 mg/dL	Intraarterial	Cardiac angiography; not in an emergency situation	. . .	. . .
Feldkamp et al, 2006 (35)	Iopromide	No; estimated glomerular filtration rate, >50 mL/min/1.73 m^2	Intraarterial	Elective coronary angiography	Standardized; 800 mL fluid given orally before procedure; 1000 mL 0.9% saline was started 30–45 min before and given until 10–12 h after procedure	No ACC or theophylline
Barrett et al, 2006 (15)	Iopamidol	Yes; ≥1.5 mg/dL serum creatinine level and/or 10–59 mL/min/1.73 m^2 creatinine clearance	Intravenous	CT	Not standardized; hydration performed—iodixanol, 66%; LOCM, 64%, P = .78; intravenous volume—iodixanol, 644 mL ± 646; LOCM, 552 mL ± 497, P = .43	No medication to prevent CIN

(Table 3 continues)

Table 3 (continued)

Trial Characteristics

Study and Year*	LOCM	Only Renal Insufficiency Patients Included†	Application Route	Procedure‡	Hydration§	Preventive Drugs‖
Rudnick, 2005 (36) ; Solomon and Rudnick, 2007 (37)	Ioversol	Yes; serum creatinine level, >1.7 mg/dL	Intraarterial	Coronary angiography	Standardized; 0.45% saline given at 100 mL/h 2–4 h before and 4 h after procedure	Randomized to receive ACC, 600 mg twice per day for 2 days; iodixanol, 67.7%; LOCM, 76.8%; $P = .1$
Sinha et al, 2004 (38)	Iohexol	Yes; >1.6 mg/dL serum creatinine level or <60 mL/min/1.73 m^2 creatinine clearance	Intraarterial	Coronary angiography with or without percutaneous coronary intervention	Standardized; 0.45% saline given at 1.5 mL/kg/h for 8 h before and 8 h after procedure	Randomized to receive oral ACC, 600 mg twice per day for 2 days; iodixanol, 43%; LOCM, 57%
Kolehmainen and Soiva, 2003 (39)	Iobitridol	Yes; patients who had severe renal impairment	Intravenous	CT	. . .	. . .
Aspelin et al, 2003 (9)	Iohexol	Yes; 1.3 or 1.5–3.5 mg/dL serum creatinine level or ≤60 mL/min/1.73 m^2 creatinine clearance	Intraarterial	Coronary, 98%, or aortofemoral, 2%, angiography; percutaneous coronary intervention— iodixanol, 17%; LOCM, 25%	Not standardized; intravenous volume— iodixanol, 977 mL ± 853; LOCM, 934 mL ± 596	. . .
Chalmers and Jackson, 1999 (40)	Iohexol	Yes; serum creatinine level, >1.7 mg/dL	Intraarterial	Renal and/or peripheral angiography	. . .	. . .
Carraro et al, 1998 (41)	Iopromide	Yes; serum creatinine level, 1.53–3 mg/dL	Intravenous	Intravenous urography	Not standardized; each patient was instructed to avoid dehydration on the day before intravenous urography	. . .
Siegle and Gavant, 1996 (42)	Iohexol	No	Intravenous	Intravenous urography	Not standardized; clear liquids orally through breakfast before intravenous urography	. . .
Lee et al, 1996 (43)	Iohexol	No	Intravenous	CT	. . .	. . .
Jakobsen et al, 1996 (44)	Iohexol	Yes; severe but stable predialytic renal failure	Intraarterial	Abdominal aortography and pelvic arteriography	Standardized; 500 mL water orally 1 h before and 1000 mL 0.9% saline administered from start of procedure	. . .
Fischbach et al, 1996 (45)	Iopamidol	No; serum creatinine level, <1.2 mg/dL	Intravenous	Intravenous angiography of abdominal aorta or lower extremity arteries	. . .	. . .
Manninen et al, 1995 (46)	Iopromide	No; patients with renal disease excluded	Intraarterial	Diagnostic cardioangiography	Not standardized; 0.9% saline administered according to routine hospital regimen	. . .

(Table 3 continues)

Table 3 (continued)

Trial Characteristics

Study and Year*	LOCM	Only Renal Insufficiency Patients Included†	Application Route	Procedure‡	Hydration§	Preventive Drugs‖
Verow et al, 1995 (47)	Iopamidol	No	Intraarterial	Aortofemoral arteriography	Fluid intake before examination was not restricted	. . .
Flinck et al, 2000 (48); Flinck et al, 1994 (49)	Iohexol	No; patients with kidney disease excluded	Intraarterial	Cardioangiography	. . .	. . .
Thorstensen et al, 1994 (50)	Iohexol	No; serum creatinine level, ≤1.58 mg/dL	Intraarterial	Femoral arteriography	. . .	. . .
Hill et al, 1994 (51)	Iohexol	No	Intraarterial	Elective diagnostic cardiac angiography	. . .	. . .
Singh et al, 1993 (52)	Iohexol	No; only patients with normal renal function	Intraarterial	Abdominal angiography	. . .	. . .
Pugh et al, 1993 (53)	Iopromide	No; only patients with no history of renal disease	Intraarterial	Aortofemoral arteriography	. . .	. . .
Klow et al, 1993 (54)	Iohexol	No; serum creatinine level, ≤1.41 mg/dL; no proteinuria	Intraarterial	Cardioangiography; patients with stable angina pectoris	. . .	. . .

* Reference 36 was not a full-text article, and references 38, 39, and 49 were published as abstracts only.

† To convert to Système International units for serum creatinine level in micromoles per liter and creatinine clearance in milliliters per second per square meter, multiply by 88.4 and 0.0167, respectively.

‡ Percentages are percentages of patients.

§ Values for intravenous volume are the mean ± standard deviation. Percentages are percentages of patients.

‖ ACC = *N*-acetylcysteine. Percentages are percentages of patients.

.22), funding source ($P = .15$), or exclusive inclusion of patients with renal insufficiency ($P = .69$) did not have a significant influence on the RR of CIN. In contrast, the use of iohexol versus the other LOCM (not iohexol) had a significant influence on the RR of CIN ($P < .01$).

Subgroup Analysis

Subgroup analysis revealed a significantly lesser risk of CIN with the use of iodixanol compared with iohexol (RR, 0.45; 95% CI: 0.26, 0.76; $P < .01$) (Fig 4a), whereas there was no difference between iodixanol and the other LOCM (RR, 0.97; 95% CI: 0.72, 1.32; $P = .86$) (Fig 4b). Two-way analysis of variance confirmed the significant effect of the use of iohexol versus the other LOCM (not iohexol) on the RR ($P < .01$) without a significant effect of the route of administration ($P = .14$) or preexisting renal insufficiency ($P = .75$). Because of borderline P values for the interaction between the use of iohexol versus LOCM that were not iohexol and the route of administration ($P = .07$) and preexisting renal insufficiency ($P = .09$), respectively, additional subgroup analyses were performed.

In none of the seven studies in which intravenous CM administration was evaluated was a reduced risk of CIN with the use of iodixanol compared with LOCM found (RR, 1.08; 95% CI: 0.62, 1.89; $P = .79$). A reduced risk of CIN was not found in studies that included patients with normal renal function (RR, 1.12; 95% CI: 0.35, 3.65; $P = .85$) or in studies that exclusively included patients with renal insufficiency (RR, 1.07; 95% CI: 0.56, 2.02; $P = .84$). Also, investigators in the study (32) that exclusively included patients with preexisting renal insufficiency and diabetes mellitus found no significant difference between iodixanol and the LOCM (RR, 0.87; 95% CI: 0.30, 2.52).

In the studies that involved evaluation of intraarterial administration of CM in which iodixanol was compared with LOCM pooled together, the RR was 0.68 (95% CI: 0.46, 1.01; $P = .06$). In studies that included patients with normal renal function after intraarterial

Table 4

Study Quality Characteristics

Study and Year*	Jadad Quality Score†	Type of Blinding	Method of Double Blinding Described and Appropriate	Randomization Process Described and Adequate	Adequate Concealed Allocation	Description of Withdrawals and Dropouts	Randomized Patients Analyzed (%)‡	Intention-to-Treat Analysis Performed	Important Baseline Differences Present	Inclusion and Exclusion Criteria Specified	Power Calculation Performed
Kuhn et al, 2008 (32)	4	Double	Yes	No	Unclear	Yes	94.3 (248/263)	No	Yes; iodine dose higher in LOCM group	Yes	No
Thomsen et al, 2008 (14)	4	Double	Yes	No	Unclear	Yes	80.4 (148/184)	No	Yes; more diabetic patients in LOCM group	Yes	No
Hardiek et al, 2008 (33)	5	Double	Yes	Yes	Unclear	Yes	83.6 (102/122)	No	Yes; iodine dose higher in LOCM group	Yes	No
Solomon et al, 2007 (12)	5	Double	Yes	Yes	Unclear	Yes	88.5 (414/468)	No	Yes; iodine dose higher in LOCM group	Yes	Yes
Schmid et al, 2007 (34)	4	Double	Yes	Yes	Unclear	No	95.0 (114/120)	Unclear	Unclear	Yes	No
Feldkamp et al, 2006 (35)	3	Double	Yes	No	Unclear	No	Unclear	Unclear	No	Yes	No
Barrett et al, 2006 (15)	5	Double	Yes	Yes	Unclear	Yes	92.2 (153/166)	No	No	Yes	No
Rudnick, 2005 (36); Solomon and Rudnick, 2007 (37)	1	Unclear	No	No	Unclear	No	Unclear	Unclear	Unclear	No	Unclear
Sinha et al, 2004 (38)	2	Double	No	No	Unclear	No	Unclear	Unclear	Unclear	No	Yes
Kolehmainen and Soiva, 2003 (39)	2	Double	No	No	Unclear	No	Unclear	Unclear	Unclear	No	Unclear
Aspelin et al, 2003 (9)	4	Double	Yes	No	Unclear	Yes	95.6 (129/135)	No	Yes; duration of diabetes mellitus and number of patients with proteinuria higher in LOCM group	Yes	Yes
Chalmers and Jackson, 1999 (40)	2	Unclear	No	No	Unclear	Yes	82.3 (102/124)	No	No	No	No
Carraro et al, 1998 (41)	2	Double	No	No	Unclear	No	Unclear	No	No	Yes	Yes
Siegle and Gavant, 1996 (42)	5	Double	Yes	Yes	Unclear	Yes	100 (150/150)	Unclear	Unclear	Yes	No
Lee et al, 1996 (43)	2	Double	No	No	Unclear	No	94.4 (119/126)	Unclear	No	No	No
Jakobsen et al, 1996 (44)	2	Double	No	No	Unclear	No	Unclear	Unclear	Yes; higher baseline serum creatinine level and lower glomerular filtration rate in LOCM group	No	No
Fischbach et al, 1996 (45)	5	Double	Yes	Yes	Unclear	Yes	98 (39/40)	No	Yes; iodine dose higher in LOCM group	Yes	No
Manninen et al, 1995 (46)	5	Double	Yes	Yes	Unclear	Yes	92.2 (119/129)	No	Yes; iodine dose higher in LOCM group	Yes	No
Verow et al, 1995 (47)	4	Double	Yes	No	Unclear	Yes	95.7 (134/140)	No	Unclear	No	No
Flinck et al, 2000 (48); Flinck et al, 1994 (49)	2	Double	No	No	Unclear	No	Unclear	Unclear	No	Yes	No
Thorstensen et al, 1994 (50)	2	Double	No	No	Unclear	No	91 (67/74)	Unclear	No	Yes	Yes

(Table 4 continues)

Table 4 (continued)

Study Quality Characteristics

Study and Year*	Jadad Quality Score†	Type of Blinding	Method of Double Blinding Described and Appropriate	Randomization Process Described and Adequate	Adequate Concealed Allocation	Description of Withdrawals and Dropouts	Randomized Patients Analyzed (%)‡	Intention-to-Treat Analysis Performed	Important Baseline Differences Present	Inclusion and Exclusion Criteria Specified	Power Calculation Performed
Hill et al, 1994 (51)	4	Double	No	Yes	Unclear	Yes	100 (200/200)	Unclear	Unclear	Yes	No
Singh et al, 1993 (52)	3	Double	No	No	Unclear	Yes	85 (51/60)	No	Yes; iodine dose higher in LOCM group	No	No
Pugh et al, 1993 (53)	4	Double	No	Yes	Unclear	Yes	5 (5/100)	No	Unclear	Yes	No
Klow et al, 1993 (54)	2	Double	No	No	Unclear	No	Unclear	Unclear	Unclear	Yes	No

* Reference 36 was not a full-text article, and references 38, 39, and 49 were published as abstracts only.

† The Jadad score is the quality score according to the Jadad et al (18) five-point scale.

‡ Numbers in parentheses were used to calculate the percentages.

CM administration, the RR was 0.82 (95% CI: 0.45, 1.51; $P = .53$); in the studies that included only patients with renal insufficiency after intraarterial CM administration, the RR was 0.59 (95% CI: 0.33, 1.07; $P = .08$). In all three studies in which iohexol was used in patients with intraarterial administration and renal insufficiency, the risk of CIN was significantly greater with iohexol than with iodixanol (RR, 0.38; 95% CI: 0.21, 0.68; $P < .01$). In contrast, the risk of CIN did not significantly differ in the two studies in which iodixanol was compared with other LOCM that were not iohexol (RR, 0.95; 95% CI: 0.50, 1.78; $P = .86$). For comparison with iopamidol, the RR was 1.26 (95% CI: 0.73, 2.19); for comparison with ioversol, the RR was 0.66 (95% CI: 0.33, 1.32). This finding was the same in the subgroup of patients with the combination of preexisting renal insufficiency and diabetes mellitus: In the study in which iohexol was used, the researchers (9) demonstrated a significantly greater risk of CIN with iohexol than with iodixanol (RR, 0.44; 95% CI: 0.22, 0.88), whereas there was no significant difference in the study (12) in which the investigators compared iodixanol and iopamidol (RR, 1.48; 95% CI: 0.66, 3.35) and in the study (36) in which the researchers compared iodixanol and ioversol (RR, 0.57; 95% CI: 0.24,1.39) in those patients.

Discussion

In our systematic review and meta-analysis, we found no significant reduction in the risk of CIN with the use of iodixanol, as compared with LOCM, pooling all studies together. Our results do not show a benefit for iodixanol after intravenous contrast medium application, with an RR of 1.08 (95% CI: 0.62, 1.89). After intraarterial CM administration, there was a borderline result because of discordant study findings, with an RR of 0.68 (95% CI: 0.46, 1.01). Subgroup and meta-regression analyses results suggest heterogeneity between the comparisons of iodixanol with iohexol and iodixanol with other

Table 5

Trial Results

Study and Year*	LOCM	Increase in Serum Creatinine Level (mg/dL)†		Occurrence of CIN			Acute Renal Failure‡	
		Iodixanol	LOCM	Definition§	Iodixanol‖	LOCM‖	Iodixanol	LOCM
Kuhn et al, 2008 (32)	Iopamidol	0.04 ± 0.26	0.04 ± 0.24	≥25%	6/123 (4.9)	7/125 (5.6)	No dialysis	No dialysis
Thomsen et al, 2008 (14)	Iomeprol	0.06 ± 0.27	−0.04 ± 0.19	≥0.5 mg/dL, ≥25%	5/72 (6.9) for both definitions	0/76 (0), 4/76 (5.3)	No dialysis	No dialysis
Hardiek et al, 2008 (33)	Iopamidol	0.028 ± 0.16	0.025 ± 0.17	≥0.5 mg/dL, ≥25%	1/54 (1.9), 7/54 (13.0)	5/48 (10.4), 10/48 (20.8)	0	1; within 24 h, patient underwent triple-bypass surgery and developed acute renal failure
Solomon et al, 2007 (12)	Iopamidol	0.12 ± 0.23	0.07 ± 0.22	≥0.5 mg/dL, ≥25%	14/210 (6.7), 26/210 (12.4)	9/204 (4.4), 20/204 (9.8)	2; no dialysis	0; no dialysis
Schmid et al, 2007 (34)	Iomeprol	0.021 ± 0.09#	0.026 ± 0.12#	≥0.5 mg/dL, ≥25%	0/58 (0), 1/58 (1.7)#	1/56 (1.8) for both definitions#	. . .	. . .
Feldkamp et al, 2006 (35)	Iopromide	0.10 ± 0.28#	0.08 ± 0.12#	≥0.5 mg/dL, ≥25%	4/105 (3.8), 9/105 (8.6)**	1/116 (0.9), 8/116 (6.9)**	. . .	. . .
Barrett et al, 2006 (15)	Iopamidol	0.04 ± 0.24	0.0 ± 0.16	≥0.5 mg/dL, ≥25%	2/76 (3), 3/76 (4)	0/77 (0), 3/77 (4)	No dialysis	No dialysis
Rudnick, 2005 (36); Solomon and Rudnick, 2007 (37)	Ioversol	0.199	0.292	≥0.5 mg/dL	12/134 (9.0)	17/125 (13.6)	. . .	. . .
Sinha et al, 2004 (38)	Iohexol	. . .	. . .	≥0.5 mg/dL	2/35 (5.7)	9/35 (25.7)	No dialysis	No dialysis
Kolehmainen and Soiva, 2003 (39)	Iobitridol	0.11 ± 0.52#	0.14 ± 0.90#	>0.5 mg/dL, >25%	4/25 (16), 3/25 (12)	4/25 (16), 3/25 (12)	. . .	. . .
Aspelin et al, 2003 (9)	Iohexol	0.13 ± 0.22	0.55 ± 0.98	≥0.5 mg/dL, ≥25%	2/64 (3), 9/64 (14)††	17/65 (26), 21/65 (32)††	0	6; 3 recovered, 2 died, 1 had persistent renal failure
Chalmers and Jackson, 1999 (40)	Iohexol	0.012 (−0.116, 0.207)‡‡	0.1 (−0.057, 0.441)‡‡	>0.5 mg/dL, >25%	5/54 (9), 2/54 (4)**	14/49 (29), 5/48 (10)**	. . .	. . .
Carraro et al, 1998 (41)	Iopromide	−0.04	−0.03	≥50%	1/32 (3)	0/32 (0)	. . .	. . .
Siegle and Gavant, 1996 (42)	Iohexol	. . .	. . .	>40% of span of reference range	7/100 (7)	3/50 (6)	. . .	. . .

(Table 5 continues)

Table 5 (continued)

Trial Results

Study and Year*	LOCM	Increase in Serum Creatinine Level (mg/dL)†		Occurrence of CIN			Acute Renal Failure‡	
		Iodixanol	LOCM	Definition§	Iodixanol‖	LOCM‖	Iodixanol	LOCM
Lee et al, 1996 (43)	Iohexol	0.02 ± 0.13§§	0.02 ± 0.31§§	. . .	. . .	. . .	. . .	. . .
Jakobsen et al, 1996 (44)	Iohexol	0.36 ± 0.57§§	1.08 ± 1.22§§	. . .	. . .	. . .	No dialysis	No dialysis
Fischbach et al, 1996 (45)	Iopamidol	0.03 ± 0.15	0.04 ± 0.07	≥0.5 mg/dL, ≥25%	1/20 (5) for both definitions#	0/19 (0), 1/19 (5)#	No changes of clinical importance	No changes of clinical importance
Manninen et al, 1995 (46)	Iopromide	−0.03 ± 0.06‖ ‖	−0.02 ± 0.07‖ ‖	. . .	. . .	. . .	. . .	. . .
Verow et al, 1995 (47)	Iopamidol	0.11 ± 0.14‖ ‖	0.13 ± 0.09‖ ‖	. . .	. . .	. . .	No changes of clinical importance	No changes of clinical importance
Flinck et al, 2000 (48); Flinck et al, 1994 (49)	Iohexol	0.03 ± 0.09#	−0.001 ± 0.08#	≥0.5 mg/dL, ≥25%	0/59 (0) for both definitions#	0/60 (0) for both definitions#	No serum creatinine level increase ≥0.5 mg/dL or ≥25%	No serum creatinine level increase ≥0.5 mg/dL or ≥25%
Thorstensen et al, 1994 (50)	Iohexol	0.09 ± 0.11§	0.06 ± 0.12§	. . .	. . .	. . .	1; increase in serum creatinine level from 1.66 to measured maximum of 4.3 mg/dL 14 d after injection, which was considered to be related to the CM	0
Hill et al, 1994 (51)	Iohexol	. . .	. . .	>0.5 mg/dL	0/101 (0)	2/99 (2)	. . .	. . .
Singh et al, 1993 (52)	Iohexol	0.14 ± 0.13‖ ‖	0.20 ± 0.18‖ ‖	. . .	. . .	. . .	No changes of clinical importance	No changes of clinical importance

(Table 5 continues)

Table 5 (continued)

Trial Results

Study and Year*	LOCM	Increase in Serum Creatinine Level (mg/dL)†		Occurrence of CIN			Acute Renal Failure‡	
		Iodixanol	LOCM	Definition§	Iodixanol‖	LOCM‖	Iodixanol	LOCM
Pugh et al, 1993 (53)	Iopromide	0.16 ± 0.12‖ ‖	0.11 ± 0.14‖ ‖	. . .	. . .	. . .	No changes of clinical importance	No changes of clinical importance
Klow et al, 1993 (54)	Iohexol	0.13 ± 0.09§	0.15 ± 0.08§	>50%	0/35 (0)	0/37 (0)	No serum creatinine level increase >50%	No serum creatinine level increase >50%

Note.—For serum creatinine level, to convert to Système International units in micromoles per liter, multiply by 88.4.

* Reference 36 was not a full-text article, and references, 38, 39, and 49 were published as abstracts only.

† Data are the mean ± standard deviation.

‡ Numbers are numbers of patients with acute renal failure.

§ The definition was based on a serum creatinine level increase as a percentage and/or as a value measured in milligrams per deciliter.

‖ Numbers were used to calculate the percentages, and percentages are in parentheses.

\# Data were missing in the original publication.

** Numbers used to calculate the percentage and the percentage for only first value were missing in the original publication.

†† Numbers used to calculate the percentage and the percentage for only second value were missing in the original publication.

‡‡ Data are the medians, and numbers in parentheses are the 1st and 3rd quartiles, respectively.

§§ Estimated standard deviation.

‖ ‖ Data from Grynne et al, 1995 (55).

LOCM (not iohexol), whereby an interaction between the use of iohexol versus other LOCM (not iohexol) and preexisting renal insufficiency is possible because of borderline *P* values. In patients with intraarterial CM administration and renal insufficiency, iohexol is associated with a greater risk of CIN than is iodixanol. In contrast, no significant difference in the risk of CIN between iodixanol and other LOCM could be found in those high-risk patients.

Our results for intraarterial CM administration seem to conflict with those of a pooled analysis of patient-level data from the iodixanol database owned by one manufacturer (GE Healthcare, Princeton, NJ), which included trials up until 2003 that suggested that intraarterial administration of iodixanol is associated with a reduced risk for CIN compared with the risk associated with LOCM (56). That analysis, however, had several important limitations. Only studies up until 2003 were evaluated, and some large trials in which the investigators showed no difference in the nephrotoxicity between iodixanol and LOCM were not included in their analysis (12,36,57). Moreover, ionic and all nonionic LOCM were pooled together in their analysis, with ionic ioxaglate (59% [789 of 1345] of patients) being the most common contrast medium used, followed by iohexol (28% [381 of 1345] of patients); only 13% (175 of 1345) of the patients received LOCM other than ioxaglate or iohexol. Thus, conclusions from that analysis may at most be drawn for the comparative nephrotoxicity of iodixanol versus ioxaglate and iohexol but not for other LOCM or for LOCM as a class.

Our finding that the use of iohexol may be associated with an increased RR of CIN in patients with renal insufficiency after intraarterial application is consistent with results of earlier pooled analyses, suggesting that the incidence of CIN with iohexol may be higher than with iodixanol and iopamidol, whereas the risk of CIN may be similar with iodixanol and iopamidol (20,21,58). Those reviews mainly pooled data from the placebo arm of studies in which researchers investi-

gated the use of CIN preventive measures, which were not randomized comparisons between two CM. Such a pooling, however, is questionable because the CIN rates are highly variable between the studies, and there is no randomization process to distribute known and unknown confounding variables equally between the CM groups. In contrast, we exclusively included trials in which the randomization was performed in regard to the CM. Moreover, only studies that employed intraarterial injection of CM were included in their reviews, making their results less generalizable than ours (21).

Osmolality of CM is widely regarded as the crucial parameter for the nephrotoxicity of CM. This assumption is based on the observation that ionic high-osmolar CM (>1500 mOsm/kg) are associated with a greater risk of CIN than are LOCM (<850 mOsm/kg) in patients with chronic kidney disease (19,59).

Figures 2, 3

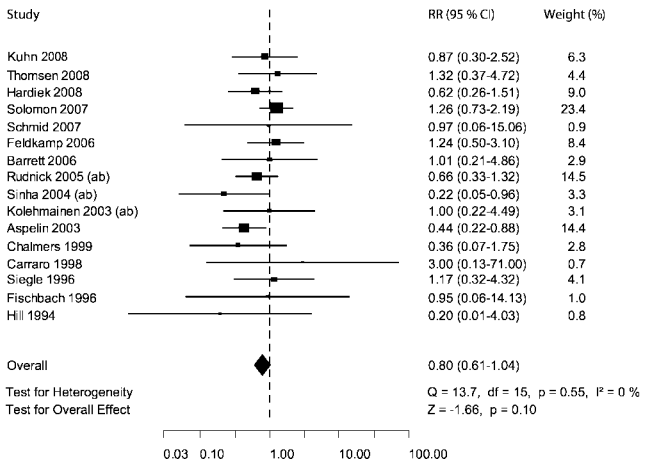


Figure 2: RR of CIN for comparison of iodixanol with all nonionic LOCM pooled together. An increase of at least 25% in serum creatinine level was used as definition for CIN when these data were available; otherwise, most closely related data given in publication were used.

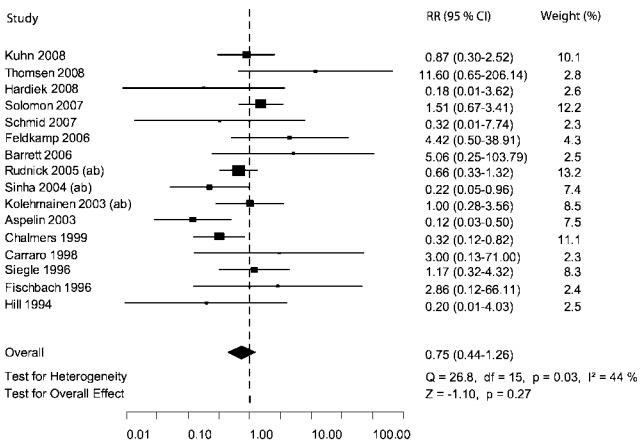
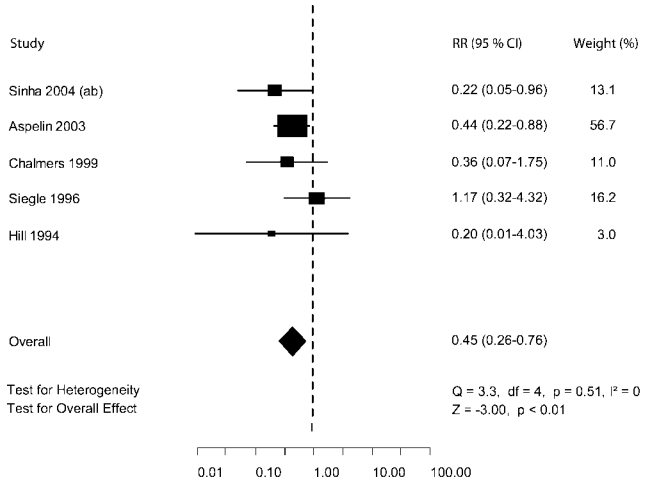
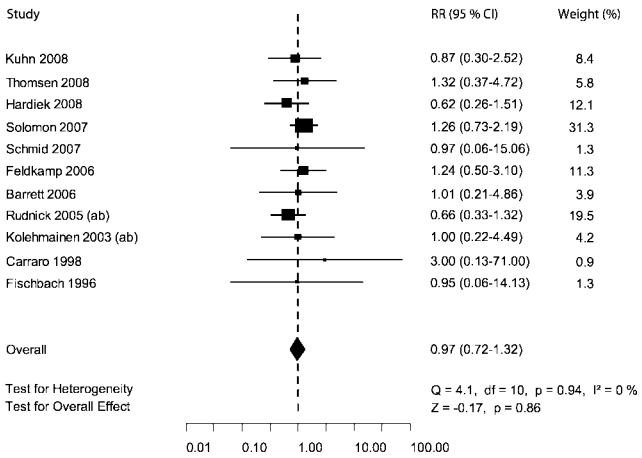


Figure 3: RR of CIN for comparison of iodixanol with all nonionic LOCM pooled together. An increase of at least 0.5 mg/dL (44.2 μmol/L) in serum creatinine level was used as definition for CIN when these data were available; otherwise, most closely related data given in publication were used.

Figure 4



a.



b.

Figure 4: **(a)** RR of CIN for comparison of iodixanol with iohexol. **(b)** RR of CIN for comparison of iodixanol with nonionic LOCM other than iohexol. Same definition for CIN as for Figure 2 was used.

Our findings that the nephrotoxicity of iso-osmolar iodixanol is not less than that of all LOCM and that the nephrotoxicity of low-osmolar iohexol seems to be different from that of other LOCM suggest that the osmolality alone does not predominantly determine the nephrotoxicity in the case of iso-osmolar CM and LOCM. Our observation is consistent with findings in experimental and clinical studies, which showed that mechanisms besides osmolality (eg, direct molecular toxicity or viscosity) play a major role in the pathogenesis of CIN with the use of LOCM or iso-osmolar CM. It was shown that there is no difference in the cytotoxicity of low-osmolar iomeprol and iso-osmolar iodixanol at equal iodine concentrations in renal proximal tubular cells in vitro, whereby the induced cytotoxicity may consist of a reversible part and an irreversible part. In addition, the viscosity of CM may play a clinically important role in CIN, especially for high-viscous iodixanol (60–64).

Our findings demonstrate that one must be cautious when interpreting results of analyses that are based on the pooling of all LOCM. Even more problems may be caused by the pooling of results from studies in which ionic LOCM were used with those from studies in which nonionic LOCM were used. We, therefore, did not include ioxaglate in our analysis, for it is an ionic dimer and, thus, is chemically different from both nonionic monomers and nonionic dimers (65,66). Whether the nephrotoxicity of ionic compounds is greater than that of nonionic compounds remains controversial, as results in previous studies are frequently confounded by differences in osmolality (8,67).

It has been suggested that the use of vigorous hydration in combination with *N*-acetylcysteine could reduce the risk of CIN, thereby eliminating any advantage of iso-osmolar CM versus LOCM in preventing CIN (68). However, since the risk of CIN is greater with iohexol than with iodixanol, even in studies in which *N*-acetylcysteine was used, and there is no difference between other LOCM and iodixanol also in studies without standardized hydration or the use of *N*-acetylcysteine, differences between the LOCM seem to play a major role in risk reduction, rather than differences in hydration and the use of *N*-acetylcysteine (14,15,33,38).

According to the *Cochrane Handbook for Systematic Reviews* (16), we included data from abstracts to minimize publication bias and to guarantee validity. In addition, we also performed our analyses without including data from abstracts; however, our results were not changed by exclusion of those data. In addition, weighting of the studies with a quality score in our statistical analysis did not affect our results.

Potential limitations of our study include the need to combine results from trials in which different definitions for CIN were used (14). We used a relative increase in serum creatinine level of more than 25% as our primary definition for CIN because this relative increase is more sensitive than an absolute increase of more than 0.5 mg/dL (44.2 μmol/L) in patients with milder degrees of renal insufficiency (serum creatinine level of less than 2 mg/dL [176.8 μmol/L]) (17). Sensitivity analyses of the different definitions for CIN and exclusion of those studies for which a particular CIN definition was not available did not change our results.

Requiring that one arm of the study include iodixanol might have created an accrual bias to assess the risk of CIN for LOCM. However, this was necessary because the aim of our study was to compare the nephrotoxicity of iodixanol with that of LOCM in randomized clinical trials.

A weakness of all meta-analyses is the use of trial-level data (eg, our analysis could not take into account the combined effect of renal insufficiency and diabetes mellitus, which is an important risk factor for CIN) (59,69). The results of our subgroup analysis, however, indicate that this factor might not be an important source of heterogeneity, because our findings also seem to be valid in this subgroup of patients.

Another potential limitation of our study was the difference in the timing of serum creatinine level measurements among the studies. In some of the early studies, there was only an early timing of serum creatinine level measurement, with measurements available only 24 hours after CM application. However, clinically significant nephropathy is unlikely to develop if the serum creatinine level does not increase by more than 0.5 mg/dL (44.2 μmol/L) or 25% within 24 hours (6,17,70).

A limitation of all of the included trials was the use of an increase in serum creatinine level (mostly >25% or >0.5 mg/dL [>44.2 μmol/L]), which is the widely accepted definition of CIN, as surrogate outcome with a paucity of data in regard to firmer end points, such as the need for dialysis or mortality. The clinical relevance of this surrogate outcome may be justified by the fact that even such a slight increase in serum creatinine level is associated with prolonged hospital stay; substantial increases in costs, morbidity, and mortality; and a worse long-term prognosis after coronary angiography (3,4,7,71–73). As a consequence, all recommendations in regard to the prevention of CIN were based on results of studies in which this surrogate outcome was used (10). However, although even modest increases in serum creatinine level after coronary angiography have been associated with a high mortality, the decline in renal function may be simply a marker for underlying comorbidity (6,8). Clinically, outcomes such as the incidence of CIN in which dialysis is required, although of considerable importance, have a low incidence following CM use (7.7 cases per 1000) (71). Thus, a well-designed, much larger multicenter trial would be necessary to achieve sufficient power to detect differences in clinically more meaningful outcomes (74).

In conclusion, results of our analysis indicate that iso-osmolar iodixanol, as compared with LOCM, is not associated with a reduced risk of CIN after intravenous application. In patients with intraarterial CM application and renal insufficiency, low-osmolar iohexol is associated with a greater risk of CIN than is iodixanol, whereas no significant difference between iodixanol and other LOCM could be found. Larger multicenter trials in which clinically relevant out-

comes are assessed are required to definitively resolve the issue about whether the nephrotoxicity of iodixanol is less than that of some of the LOCM after intraarterial application in high-risk patients.

Appendix A

With regard to data sources and search strategy, we conducted a systematic literature search of MEDLINE (1950 through August 2007), EMBASE (1974 through August 2007), BIOSIS (1975 through August 2007), Web of Science, ISI Web of Knowledge, Citation Databases: Science Citation Index Expanded (1987 through August 2007), Current Contents Medizin (2007), and the Cochrane Library (2007). We derived three comprehensive search themes that were then combined by using the Boolean operator AND. *(a)* For the theme "iodixanol," we used combinations of the following terms as Medical Subject Headings and text words: "contrast media," "contrast medium," "contrast dye," "radiographic contrast," "radiocontrast media," "radiocontrast medium," "contrast agent*," "dimer," "dimeric," "isoosmola*," "iso-osmola*," "iodixanol," and "Visipaque." *(b)* For the theme "nephrotoxicity," the following terms were used: "nephritis," "nephropath*," "nephrotoxic*," "kidney," "renal," "creatinine," "adverse effect*," "adverse event*," and "side effect*." *(c)* We used the Cochrane Highly Sensitive Search Strategy for randomized controlled trials (16).

We searched trial registers on the Internet; abstracts from major radiologic, nephrologic, and cardiological scientific meetings from 2003 to 2007 (we expected that good-quality abstracts presented before this time would have been published by 2007); and reference lists of all relevant studies. Experts in the field were also consulted. The manufacturers of CM were contacted with a request for information about any relevant studies as yet unpublished, in progress, or unidentified by using the previously mentioned search strategies.

Appendix B

For data extraction and quality assessment, two investigators extracted data from all primary studies that fulfilled the eligibility criteria with use of a standardized form. Discordances were resolved in consensus. Recorded data variables were as follows: first author's name, year of publication, source of publication, type of blinding, total number of individuals, mean age, percentage of female subjects, percentage of individuals with diabetes mellitus, baseline serum creatinine concentration, contrast medium dose, type of diagnostic or therapeutic procedure and route of contrast medium application, type of LOCM, use of periprocedural hydration, specific definition of CIN, funding source, changes in serum creatinine concentration, and number of patients with a decrease in renal function for each contrast medium group. For studies in which there was more than one LOCM or iso-osmolar contrast medium group (eg, different iodine concentrations of iodixanol), the results of all groups were pooled as a single comparative group.

The primary outcome measures were the incidence of CIN and change in serum creatinine levels. When possible, we used the mean peak changes in serum creatinine level after a dose of contrast medium within 3 days. We used an increase in serum creatinine level of more than 25% as our primary definition for CIN (17). If these data were unavailable, we used the most closely related data given in the publication. For sensitivity analysis, we repeated the analysis after exclusion of those studies for which data for the 25% definition of CIN were unavailable. Furthermore, we used an increase in serum creatinine level of more than 0.5 mg/dL (44.2 μmol/L) as a definition for CIN if these data were available; otherwise, we used the most closely related data given in the publication and repeated the analysis after exclusion of those studies for which data for the 0.5 mg/dL (44.2 μmol/L) definition were unavailable.

Two investigators independently evaluated details of the methodological quality of the included trials that were likely to influence internal and external validity: method of blinding, method of randomization, allocation concealment, reporting of dropouts and withdrawals, number of randomized patients who were not included in the analysis, evidence of important baseline differences, specification of inclusion and exclusion criteria, intention-to-treat analysis, and power calculation. To determine an overall quality score, the validated five-point scale of Jadad et al (18) was used. The scale consists of three items that describe randomization (0–2 points), masking (0–2 points), and dropouts and withdrawals (0–1 point) in the report of the trials (18). At least two attempts were made to contact the first and/or senior author or the contrast medium manufacturer that was supporting the relevant study to provide data that were missing in the original publication. Missing data were provided for 10 trials (Tables 2 and 5).

Before we performed the analysis, we proposed several hypotheses, both as potential explanations for any heterogeneity that might be observed among the study results and as secondary questions to be answered. A benefit from the use of iso-osmolar CM may only exist in patients with preexisting renal impairment (19). Thus, a subgroup analysis for subjects with normal and impaired renal function prior to administration of contrast material was performed. Because the nephrotoxicity of iohexol may be greater than that for other nonionic LOCM (20,21), a subgroup analysis for iohexol and LOCM other than iohexol was performed. Also, a subgroup analysis for intraarterial contrast medium application in patients with chronic renal insufficiency was performed, because a beneficial effect of iso-osmolar CM may be confined to those patients (19).

Appendix C

In regard to data synthesis and analysis, the baseline characteristics were compared with the Wilcoxon rank sum test. For each trial, we calculated the RR of CIN and the difference in the increase in serum creatinine level between trial groups. Meta-analysis was performed

by using the random-effects model of DerSimonian and Laird (22) to obtain pooled RRs, pooled differences in serum creatinine level increase (weighted mean differences), and associated 95% CIs for outcomes. The random-effects method of DerSimonian and Laird (22) was applied because it works independent of heterogeneity and coincides with the inverse variance fixed-effects method if there is no heterogeneity. Statistical heterogeneity of trial results was tested with the Cochran Q statistic and also was expressed as I^2, which indicates the percentage of the variability in effect estimates that was caused by heterogeneity rather than chance (23). Sensitivity analyses were performed by means of repetition of the analysis with a fixed-effects model (Mantel-Haenszel test) if we detected no heterogeneity across studies, after *(a)* exclusion of studies for which no data for the particular definition of CIN were available, *(b)* after exclusion of studies that were not published as full-text articles, and *(c)* after weighting of the studies with a quality weight (24) that was the product of the precision (ie, inverse variance) and the quality score of Jadad et al (18).

We performed subgroup analysis, meta-regression analysis for continuous variables, and one-way analysis of variance for categorical variables to assess the effect of baseline serum creatinine level, age, percentage of female subjects, percentage of diabetic individuals, contrast medium dose, application route, funding source, presence of chronic kidney disease, and the use of iohexol versus the other nonionic LOCM (25). In each meta-regression analysis and one-way analysis of variance, the RR of CIN or the difference in the increase in serum creatinine level was the dependent variable and one of the study characteristics was the independent variable. Two-way analysis of variance ($n = 2$) was performed to investigate the effect of the use of iohexol versus the other LOCM on the RR with regard to possible interactions with the route of administration or preexisting chronic kidney disease. In each analysis of variance, the studies were weighted as in meta-regression analysis. We examined the data for potential publication bias by using the Egger and Begg tests, as well as the Begg funnel plot in which log RRs were plotted against their corresponding standard errors (26,27).

All P values were two sided and differences with P values of less than .05 were regarded as significant. For the Q statistics, a difference with a P value of less than .1 was considered significant. For studies in which no events in one of the trial groups were reported, the well-known half-integer correction was applied to calculate the RR. Studies with no events at all were excluded from the RR analyses. The standard deviations for the mean increase in serum creatinine level in the studies by Jakobsen et al (44) and Lee et al (43) were not available in the original reports or from the authors. The standard deviations for those two studies were estimated according to the method of imputing standard deviations for changes from baseline described in the *Cochrane Handbook for Systematic Reviews of Interventions* (28). All statistical analyses were performed with a system for statistical computing (R system, version 2.4.1, 2006; R Development Core Team, Vienna, Austria).

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