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Ionic Low-Osmolar Versus Nonionic Iso-Osmolar Contrast Media to Obviate Worsening Nephropathy After Angioplasty in Chronic Renal Failure Patients

The ICON (Ionic versus non-ionic Contrast to Obviate worsening Nephropathy after angioplasty in chronic renal failure patients) Study

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Objectives This randomized, prospective, double-blind, multicenter study compared nephrotoxicity of the nonionic iso-osmolar contrast media (CM) iodixanol versus the ionic low-osmolar CM ioxaglate in patients with chronic renal insufficiency undergoing coronary angiography.

Background The properties of iodinated CM might contribute to the incidence of contrast-induced nephropathy (CIN).

Methods Patients with renal impairment undergoing coronary angiography were randomly assigned to iodixanol (n = 72) or ioxaglate (n = 74).

Results Baseline characteristics were well-matched between the 2 groups. The predicted risk score for CIN was similar in the iodixanol and in the ioxaglate groups (11.9 ± 4.1 vs. 11.8 ± 4.1), as was the use of N-acetylcysteine (70% vs. 73%). The primary end point of the study, median peak increase of serum creatinine from day 0 through day 3 after angiography, did not differ between the iodixanol (0.09 mg/dl; interquartile range 0.00 to 0.30 mg/dl) and the ioxaglate (0.15 mg/dl; interquartile range 0.00 to 0.40 mg/dl; p = 0.07) groups. The percentages of patients with a peak increase of serum creatinine ≥0.5 mg/dl (15.9% in iodixanol vs. 18.2% in ioxaglate), ≥1.0 mg/dl (1.4% vs. 4.5%), and ≥25% or ≥0.5 mg/dl (15.9% vs. 24.2%, respectively) also did not differ significantly between the 2 groups.

Conclusions In high-risk patients undergoing coronary angiographic procedures, use of the nonionic iso-osmolar CM iodixanol does not reduce renal deterioration in patients with renal impairment, compared with the ionic low-osmolar CM ioxaglate. Given that the study was underpowered to compare nephrotoxicity of the 2 groups under the active medical protection of CIN, a larger randomized study is warranted that will enroll patients with higher risks of CIN under a strict control of hydration regimens and adjunctive medications. (J Am Coll Cardiol Intv 2009;2:415–21) © 2009 by the American College of Cardiology Foundation

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The continuing growth in diagnostic imaging and percutaneous coronary intervention increases the number of patients exposed to iodinated contrast agents (1). Contrast-induced nephropathy (CIN) is the third most common cause of renal failure and is associated with morbidity and mortality after coronary catheterization (1–4). The typical clinical feature of CIN is a transient rise in serum creatinine beginning within 24 h of contrast media (CM) administration, typically reaching a peak within 2 to 3 days and returning to baseline within 2 weeks (2).

The most important risk factor for CIN is pre-existing chronic renal insufficiency (3). Several other risk factors for CIN have been identified, and a risk scoring has been proposed (3–6). The properties of iodinated CM might contribute to the incidence of CIN (5,7–15). As compared with ionic high-osmolar CM, nonionic low-osmolar contrast media (LOCM) have been associated with less deterioration of renal function after angiography in patients with chronic renal impairment (7–10,16). Iodixanol (Visipaque, Nycomed Amersham, Princeton, New Jersey) is the only available agent in the class of nonionic iso-osmolar contrast media (IOCM) and has been favorably compared with nonionic LOCM for renal protection (17,18). Some studies have suggested that IOCM have a lower risk than LOCM, but the etiology of CIN is complex and multifactorial, and study results have been conflicting (9,11–15,19). Therefore, further research is needed to investigate the extent to which IOCM and LOCM differ in nephrotoxic potential.

Abbreviations and Acronyms

CIN = contrast-induced nephropathy

CM = contrast media

IOCM = iso-osmolar contrast media

LOCM = low-osmolar contrast media

Ioxaglate is the only ionic LOMC agent. Several experimental studies on the properties of ionic contrast media indicated reduced thrombogenicity (20,21), but these studies were not corroborated in clinical investigation (22). Therefore, it is unclear how the ionic and lower viscous properties of the LOMC ioxaglate relate to CIN risk compared with the IOCM iodixanol.

The ICON (Ionic versus non-ionic Contrast to Obviate worsening Nephropathy after angioplasty in chronic renal failure patients) study compared the nephrotoxicity of the nonionic IOCM iodixanol (Visipaque) with that of the ionic LOCM ioxaglate (Hexabrix, Mallinckrodt, Hazelwood, Missouri) in high-risk patients with stable chronic renal insufficiency undergoing percutaneous diagnostic or interventional procedures using CM.

Methods

Study population and procedures. This was a randomized, prospective, controlled, double-blinded multicenter study at 7 centers in the U.S. and Canada (Appendix). For inclusion, patients were at least 18 years old, scheduled for coronary angiography, and had stable renal insufficiency defined as having 2 consecutive stable serum creatinine values (>1.5 mg/dl [132.6 μmol/l] and ≤3.0 mg/dl [265.2 μmol/l]), with the most recent obtained within 24 h before angiography. The patients were willing and able to return to an acceptable laboratory facility at 48 to 72 h after the procedure for laboratory evaluations. Exclusion criteria were pregnancy, lactation, left ventricular ejection fraction <20%, hemodynamic instability, acute myocardial infarction, planned staged interventional procedures, participation in any investigational drug study within 30 days before enrollment, allergy to iodinated CM, severe liver disease, jaundice or hematological disease, scheduling for renal angiography, planned exposure to any CM within 72 h after the procedure, intravascular administration of CM within the previous 5 days, inability or reluctance to return to an acceptable laboratory facility at 48 to 72 h after the procedure, current intake of nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs except acetylsalicylic acid, phenylbutazone, aminoglycosides, amphotericin B, polymicin, platinum complexes), and acute deterioration or fluctuation of renal function. This study was conducted in compliance with the principles of Good Clinical Practice regulations, and the protocol was approved by the institutional review board of each institution. Written informed consent was obtained from each patient before enrollment.

Patients were randomly assigned to receive either the nonionic IOCM iodixanol or the ionic LOCM ioxaglate (1:1) with sealed envelopes that contained a computer-generated randomization sequence. N-acetylcysteine was administered at the discretion of the investigator. Patients received diphenydramine 25 mg intravenously before the procedure as well as intravenous one-half isotonic saline at 100 ml/h for at least 3 to 5 h before the index procedure, throughout the angiographic-interventional procedure, and for at least 12 h after CM administration (or until discharge if it occurred sooner). Sodium bicarbonate was not used. Invasive angiography or percutaneous coronary intervention was performed according to the normal practice of the participating institutions. Serum creatinine was monitored before injection of CM as well as at 12, 24, and 48 to 72 h after injection. Creatinine clearance was estimated from serum creatinine with the Cockcroft-Gault formula (23). A change in post-injection serum creatinine values of 0.5 mg/dl (44.2 μmol/l) or >25% of the baseline values was classified as in-hospital acute renal failure and followed until the serum creatinine value returned to within 5% of the baseline value or was stable for a period of at least 14 days. All patients had an electrocardiogram on baseline, immediately after procedure, and on the day of discharge. Cardiac enzymes were serially collected at baseline as well as at 6, 12, 24, and 48 to 72 h after procedure.

End points and definitions. The primary end point of the study was the median peak increase in serum creatinine concentration between day 0 (when CM was administered)

and day 3. To assess actual deterioration of renal function, a decrease of serum creatinine from baseline was considered "zero increase" of serum creatinine. The secondary end points included: the proportion of patients with a peak serum creatinine increase of ≥0.5 mg/dl (44.2 μmol/l); the proportion of patients with a peak serum creatinine increase of ≥1.0 mg/dl (88.4 μmol/l); and the proportion of patients with a peak serum creatinine increase of either ≥0.5 mg/dl or ≥25% from day 0 through day 3. Acute renal failure (with or without dialysis) was defined as a rise in serum creatinine ≥25% above the baseline value in the initial 3 days after the index procedure. Non–Q-wave myocardial infarction was defined as a creatine kinase-myocardial band enzyme elevation 3 times the upper normal value without new Q waves on the electrocardiogram. A Q-wave myocardial infarction was defined as presence of new pathologic Q waves (>0.04 s) on an electrocardiogram in conjunction with an elevation in creatine kinase greater than twice the normal value. The predicted risk score of CIN was assessed on the basis of the patients' clinical and laboratory conditions as previously proposed (3). All adverse clinical events as well as study end points were monitored and adjudicated by the independent event committee.

Statistical methods. A total sample size of 130 patients was calculated to have an 80% power to detect a difference of 0.5 SD in the mean peak serum creatinine concentrations between the 2 study groups. In relative terms, 0.5 SD is generally considered to be a moderately small difference. With data from the NEPHRIC (Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media) study (13), which reported the SD of the peak change in mean serum creatinine as 0.22 to 0.98 mg/dl, the present study was designed to have an 80% power to detect differences in the range of 0.11 to 0.49 mg/dl in peak serum creatinine between the 2 groups. During the enrollment into the study, the sample size was further increased to 145 patients to allow for loss to follow-up.

Continuous variables are presented as mean ± SD or median with interquartile range (IQR) and compared with the Student unpaired *t* test or Wilcoxon rank sum tests when the distribution was not normally distributed. Categorical variables are presented as numbers or percentages and were compared with chi-square or Fisher exact tests when there were <5 values in a given cell. The primary end point was analyzed with the Wilcoxon rank sum test, due to the skewed distribution of the primary study end point. In addition, a parametric *t* test with a normalizing logarithmic transformation was conducted for comparison, with no significant differences compared with the nonparametric Wilcoxon rank sum test. A correction factor of 0.1 was added to each value before applying the log transform to deal with zero values of the primary end point. Relative risks were analyzed for binary secondary end points. All tests were 2-sided at a significance level of 0.05. All statistical analyses were carried out with SAS software version 9.1 (SAS institute, Cary, North Carolina).

Results

Baseline characteristics and procedures. A total of 146 patients were enrolled over a period of 3 years: 72 patients received iodixanol and 74 patients received ioxaglate as randomly allocated. Adherence to randomization assignment was 100%. The 2 groups had similar demographic and baseline characteristics as shown in Tables 1 and 2. Baseline creatinine clearance was 44.5 ± 14.1 ml/min in the iodixanol group and 45.9 ± 18.9 ml/min in the ioxaglate group (p = NS). N-acetylcysteine was administered to 72% of patients. A predicted mean risk score of CIN was 11.9 ± 4.1 in the iodixanol group and 11.8 ± 4.1 in the ioxaglate group (p = NS). High volumes of contrast agent (over 200 ml) were administered in 56% of the iodixanol group and in 51% of the ioxaglate group. Both groups were similarly well-hydrated, with mean fluid intake of 3.6 l in the iodixanol group and 3.8 liters in the ioxaglate group.

Increase of serum creatinine. The peak increase in serum creatinine over time did not differ significantly between the 2 groups: the primary end point, median increase from baseline to day 3, was 0.09 (IQR: 0.00 to 0.30) in the iodixanol group versus 0.15 (IQR: 0.00 to 0.40) in the ioxaglate group (p = 0.07); and mean respective values were 0.20 ± 0.34 mg/dl in the iodixanol group and 0.35 ± 0.76 mg/dl in the ioxaglate group (p = 0.14) (Table 3).

The values of serum creatinine at baseline, 12 h, 24 h, and 72 h were not statistically different between the 2 groups (Fig. 1). However, the change in serum creatinine from baseline to day 3 was lower in patients who were administered iodixanol (mean: 0.12 ± 0.40 mg/dl vs. 0.31 ± 0.78 mg/dl, p = 0.083; median: 0.09; IQR: −0.10 to 0.30 vs. median: 0.15; IQR: 0.00 to 0.40, p = 0.035). There were no significant differences in the incidences of any of the secondary end points between the 2 groups (Table 3). In-hospital acute renal failure occurred with similar incidences in the iodixanol (11.1%) and the ioxaglate (17.6%) groups (relative risk: 0.63; 95% confidence interval: 0.28 to 1.43; p = 0.35).

Adverse events. During hospital stay and out to 30 days after the index procedure, the incidences of adverse events in terms of death, myocardial infarction, and repeat revascularization did not differ between the 2 groups (Table 4). Allergic reactions to CM developed in 5.4% (n = 4) in the ioxaglate group and in none of the patients in the iodixanol group (p = 0.12).

Discussion

The primary finding of this study is that the use of nonionic IOCM iodixanol was not associated with a smaller increase

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Table 1. Baseline Characteristics

	Iodixanol (n = 72)	Ioxaglate (n = 74)	p Value
Age (yrs)	71.6 ± 9.9	71.3 ± 12.3	0.86
Male	87.5	87.8	1.00
History of coronary artery disease	76.4	78.4	0.84
Unstable angina	30.6	32.4	0.86
History of myocardial infarction	44.4	39.2	0.62
History of bypass surgery	34.7	25.7	0.28
History of percutaneous coronary intervention	50.0	38.4	0.18
History of smoking	70.8	51.4	0.02
Hypertension	88.9	86.5	0.80
Hyperlipidemia	86.1	78.4	0.28
Diabetes mellitus	51.4	40.5	0.25
Peripheral vascular disease	33.3	20.3	0.09
History of cerebrovascular accident	22.2	13.5	0.19
History of congestive heart failure	25.4	25.7	1.00
History of exposure to contrast agent	73.6	74.3	1.00
History of contrast-induced nephropathy	2.8	1.4	0.62
Left ventricular ejection fraction	50.9	49.3 ± 12.2	0.43
Baseline serum creatinine (mg/dl)	1.86 ± 0.34	1.80 ± 0.29	0.23
Baseline creatinine clearance (ml/min)	44.5 ± 14.1	45.9 ± 18.9	0.64
Predictive CIN risk score	11.9 ± 4.1	11.8 ± 4.1	0.94

Data are mean ± SD or %.
CIN = contrast-induced nephropathy.

in the peak creatinine value compared with the use of ionic LOCM ioxaglate in patients with chronic renal impairment who underwent coronary angiography. However, the mean peak change in serum creatinine from baseline to day 3 was significantly lower in patients who were administered iodixanol.

There is now a consensus that CIN can be defined as an absolute rise in serum creatinine of 0.5 mg/dl or more or a relative rise of 25% or more from baseline at 48 to 72 h after exposure to CM, in the absence of an alternative explanation for the rise (6). The recent Contrast-Induced Nephropathy Consensus Panel recommended using a relative increase in serum creatinine to measure CIN, because this is less sensitive to the initial level of renal function at baseline than an absolute increase (24). Because both absolute and relative increases have been widely used as definitions of CIN in published studies, we reported the rates of several different definitions of CIN in the present study to allow comparison with previous work. The choice of 48 to 72 h as the window for the last serum creatinine measurement in the present study followed the recommendation of Contrast-Induced Nephropathy Consensus Panel (24).

Table 2. Medications Related to Index Procedure

	Iodixanol (n = 72)	Ioxaglate (n = 74)	p Value
N-acetylcysteine	70.8	73.0	0.85
Hydration (l)	3.61 ± 3.33	3.78 ± 3.12	0.77
Oral	1.03 ± 1.27	1.54 ± 1.73	0.06
Intravenous	2.94 ± 3.19	2.77 ± 2.59	0.73
Amount of contrast media (ml)	215 ± 123	204 ± 108	0.55
<100	12.5	19.2	0.36
≥100 and <200	31.9	30.1	0.86
≥200 and <300	38.9	30.1	0.29
≥300	16.7	20.5	0.67
Duration of contrast administration (min)	51.14 ± 33.06	48.1 ± 35.5	0.59
Percutaneous coronary intervention	66.7	64.9	0.86

Data are mean ± SD or %.

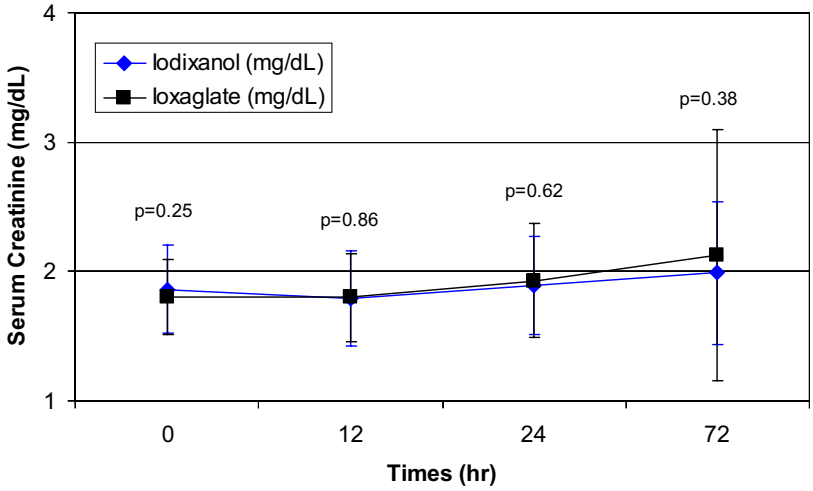
Table 3. Peak Increase of Serum Creatinine Between Day 0 and Day 3

	Iodixanol	Ioxaglate	Difference (95% CI)	Relative Risk (95% CI)	p Value
Peak increase in serum creatinine (mg/dl), median (IQR)	0.09 (0.00 to 0.30)	0.15 (0.00 to 0.40)	NA	NA	0.07*
Log-transformed peak increase in serum creatinine with +0.1 factor, mean ± SD	−1.61 ± 0.82	−1.34 ± 0.93	−0.27 (−0.56 to 0.03)	NA	0.08†
Patients with increase in serum creatinine, %					
≥0.5 mg/dl	15.9	18.2	−2.2% (−16.5 to 12.0)	0.88 (0.42 to 1.85)	0.82
≥1.0 mg/dl	1.4	4.5	−3.1% (−10.4 to 4.2)	0.32 (0.03 to 2.99)	0.36
≥25%	15.9	24.2	−8.3% (−23.4 to 6.8)	0.66 (0.33 to 1.31)	0.28
≥25% or ≥0.5 mg/dl	15.9	24.2	−8.3% (−23.4 to 6.8)	0.66 (0.33 to 1.31)	0.28

*p value with Wilcoxon rank sum test. †p value with Student *t* test.
CI = confidence interval; IQR = interquartile range.

Because the incidence of CIN was <2% in general population, randomized studies comparing nephrotoxicities of iodixanol with LOCMs have included patients at an increased risk of CIN and used limited amount of CM (12,13,15). The present study also involved the patients with renal impairment at a high risk of CIN. The baseline mean value of serum creatinine (1.83 mg/dl), prevalence of diabetes mellitus (46%), average amount of CM administered >200 ml, and predictive CIN risk score (3) were all similar or higher than in previous randomized studies (12,13,15). This should not be interpreted as a liberal CM volume use but as treatment of complex patients that necessitated use of higher CM volume despite conservation measures. The rates of acute renal failure (18% to 22% during hospital stay) in the present study are consistent with this high-risk profile of the study population (3).

The reason for the present finding that the use of iodixanol did not result in a smaller increase of creatinine as compared with the ioxaglate is not certain. One of the possible explanations is that ICON was underpowered to compare a nephrotoxicity of the 2 groups. In addition, because the studies had different protocols and definitions, the results of our study cannot be directly compared with those of previous studies. Another plausible explanation is that LOCM and IOCM affect renal function to a similar degree. The recently published randomized CARE (Cardiac Angiography in Renally Impaired Patients) study (25), supported this hypothesis, finding that the incidence of serum creatinine ≥25% was 12.4% in 210 iodixanol patients and 9.8% in 204 LOCM iopamidol patients (p = 0.44). Similarly, in a subset analysis of the randomized CONTRAST (Fenoldopam Mesylate for the Prevention of



	0	12	24	72
Iodixanol (mg/dL)	1.86 ± 0.34	1.79 ± 0.37	1.89 ± 0.38	1.99 ± 0.55
Ioxaglate (mg/dL)	1.80 ± 0.29	1.80 ± 0.34	1.93 ± 0.44	2.13 ± 0.97

Figure 1. Mean Values of Serum Creatinine at Baseline, 12 H, 24 H, and Between 24 and 72 H After the Index Procedure

The values were not statistically different as assessed by Student *t* test between the iodixanol and ioxaglate groups at each period. The p values are 0.083 and 0.035 for the mean and median change in serum creatinine from baseline to day 3 between the iodixanol and ioxaglate groups, respectively.

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Table 4. In-Hospital and 30-Day Adverse Clinical Events

In-Hospital Events	Iodixanol (n = 72)	Ioxaglate (n = 74)	p Value
Death	2 (2.8%)	0 (0%)	0.24
Cardiac	1 (1.4%)	0 (0%)	0.49
Renal	0 (0%)	0 (0%)	—
Other	1 (1.4%)	0 (0%)	0.49
Myocardial infarction	0 (0%)	1 (1.4%)	1.00
Q-wave	0 (0%)	0 (0%)	—
Non–Q-wave	0 (0%)	1 (1.4%)	1.00
Repeat revascularization	1 (1.4%)	0 (0%)	0.49
Percutaneous	0 (0%)	0 (0%)	—
Bypass surgery	1 (1.4%)	0 (0%)	0.49
Overall events	3 (4.2%)	1 (1.4%)	0.36
30-Day Events	**(n = 70)**	**(n = 74)**	
Death	4 (5.7%)	1 (1.4%)	0.20
Cardiac	3 (4.3%)	1 (1.4%)	0.36
Renal	0 (0%)	0 (0%)	—
Other	1 (1.5%)	0 (0%)	0.49
Myocardial infarction	0 (0%)	1 (1.4%)	1.00
Q-wave	0 (0%)	0 (0%)	—
Non–Q-wave	0 (0%)	1 (1.4%)	1.00
Revascularization	2 (2.9%)	1 (1.4%)	0.61
Percutaneous	1 (1.4%)	0 (0%)	0.49
Bypass surgery	1 (1.4%)	1 (1.4%)	1.00
Overall events	6 (8.6%)	3 (4.2%)	0.32

Data are n (%).

Contrast-Induced Nephropathy) trial, the incidence of CIN was similar with IOCM iodixanol compared with LOCM agents (33.3% vs. 25.3%; p = 0.39) (26).

However, in the NEPHRIC (Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media) study, among 129 patients with diabetes and baseline renal insufficiency undergoing cardiac and aorto-femoral angiography, iodixanol was associated with significantly lower rates of CIN than iohexol (13). Use of a different LOCM (iohexol, having osmolarity higher than of ioxaglate [780 mOsm/kg vs. 580 mOsm/kg]) for the control group in assessing the benefit of iodixanol might have contributed to the outcomes of that study. The incidence of a serum creatinine increase ≥1.0 mg/dl was 15% in the iohexol group (control of the NEPHRIC study), but the incidence was 4.5% in the iodixanol group (control of the present study). The iodixanol groups, however, did not show a striking difference in the incidence of the serum creatinine increase ≥1.0 mg/dl between the NEPHRIC trial (0%) and the present study (1.5%) (13). Furthermore, definitions of the primary end point in the 2 studies were not the same. Whereas the primary end point of the NEPHRIC study was based on the absolute change in serum creatinine from baseline to peak, the primary end point of the present study was the peak increase in serum creatinine from baseline. However, as noted, the absolute change in serum creatinine in our study was significantly less in the iodixanol group, consistent with the NEPHRIC study.

More recently, the RECOVER (REnal toxicity evaluation and COmparison between Visipaque and HExabrix in patients with Renal insufficiency undergoing coronary angiography) study, which used the same CM as our study, presented a less nephrotoxic effect of the iodixanol than the ioxaglate in 300 patients with renal impairment (15). The incidence of CIN, defined as an increase of serum creatinine ≥25%, was 7.9% in the iodixanol group and 17.0% in the ioxaglate group (p = 0.021). There was an interesting difference in the protocols between the 2 randomized studies (RECOVER and NEPHRIC) and the present study. Only 8.5% of patients in the NEPHRIC study and none in the final analysis of the RECOVER study were treated with N-acetylcysteine. In our study, however, the drug was administered to 72% of patients. Although the data on N-acetylcysteine are not yet substantial enough to warrant strong recommendation of the drug in national guidelines, the benefit in preventing CIN has been reported in several randomized trials and meta-analyses (27–29). Therefore, a less restricted use of N-acetylcysteine in the present study might have had an effect on the result. The randomized CARE study (25) and a registry study (14), which did not avoid use of N-acetylcysteine, showed a similar incidence of CIN with either iodixanol or LOCMs.

Vigorous hydration before and after the procedure in the present study might further affect outcomes. Prophylactic intravenous saline hydration, beginning 12 h before CM exposure, has been shown to reduce the incidence of CIN (5). Patients in the present study were hydrated with one-half normal saline before, during, and after the procedure, receiving a mean of approximately 3.7 l of fluid in total. In contrast, the patients in the NEPHRIC study received a mean intravenous fluid <1 l (13). In the RECOVER study, patients received saline hydration at 1 ml/kg/h for at least 8 h before and after the procedure, but no data were presented to show whether the volume of hydration was equivalent between the 2 treatment groups (15).

The use of a central core biochemistry laboratory to measure serum creatinine would certainly strengthen the conclusions of the study. Also, there is still a possibility that the present study was underpowered to compare a nephrotoxicity of the 2 groups under the active medical protection of CIN. This limitation coupled with the diversity in results among the NEPHRIC, RECOVER, CARE, and ICON trials warrants a new randomized study in which more patients with higher risks of CIN are enrolled under a strict control of hydration regimens and adjunctive medications.

Conclusions

The results of the present study indicated that use of the nonionic IOCM iodixanol might not reduce renal deterio-

ration in patients with renal impairment after coronary angiography compared with the ionic LOCM ioxaglate. It remains important that a combined approach with low-dose CM, use of N-acetylcysteine, adequate hydration, and discontinuation of nephrotoxic agent is considered in patients at a high risk of CIN.

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Key Words: angiography ■ contrast media ■ renal insufficiency.

APPENDIX

STUDY CENTERS AND INVESTIGATORS

Center (Number of Enrolled Patients)	Investigator
Lenox Hill Hospital, New York, NY (50)	Roxana Mehran, MD
Columbia University Hospital, New York, NY (44)	George D. Dangas, MD, PhD
Scripps Clinic, San Diego, CA (19)	Paul S. Teirstein, MD
Weill-Cornell Medical College, New York, NY (10)	S. Chiu Wong, MD
Moses Cone Heart and Vascular Center, Greensboro, NC (13)	William E. Downey, MD
St. Michaels Hospital, Toronto, Ontario, Canada (8)	Wayne B. Batchelor, MD, MHS
LDS Hospital, Salt Lake City, UT (2)	Peter J. Casterella, MD