**OBJECTIVES**

This study sought to compare the nephrotoxicity of iodixanol and ioxaglate in patients with renal impairment undergoing coronary angiography.

**BACKGROUND**

Iodixanol, a nonionic, dimeric, iso-osmolar contrast medium (IOCM), may be less nephrotoxic than low-osmolar contrast media (LOCM) in high-risk patients.

**METHODS**

In a prospective, randomized trial in 300 adults with creatinine clearance (CrCl) ≤ 60 ml/min, patients received either iodixanol or ioxaglate and underwent coronary angiography with or without percutaneous coronary intervention. The primary end point was the incidence of contrast-induced nephropathy (CIN) (an increase in serum creatinine [SCr] ≥ 25% or ≥ 0.5 mg/dl [≥ 44.2 μmol/l]). The incidence of CIN in patients with severe renal impairment at baseline (CrCl < 30 ml/min) or diabetes and in those receiving large doses (≥ 140 ml) of contrast medium was also determined.

**RESULTS**

The incidence of CIN was significantly lower with iodixanol (7.9%) than with ioxaglate (17.0%; p = 0.021), corresponding to an odds ratio (OR) of CIN of 0.415 (95% confidence interval [CI] 0.194 to 0.889) for iodixanol. The incidence of CIN was also significantly lower with iodixanol in patients with severe renal impairment (p = 0.023) or concomitant diabetes (p = 0.041), or in patients given ≥ 140 ml of contrast media (p = 0.038). Multivariate analysis identified use of ioxaglate (OR 2.65, 95% CI 1.11 to 6.33, p = 0.028), baseline SCr, mg/dl (OR 2.0, 95% CI 1.04 to 3.85, p = 0.038), and left ventricular ejection fraction, % (OR 0.97, 95% CI 0.94 to 0.99, p = 0.019) as independent risk factors for CIN.

**CONCLUSIONS**

The IOCM iodixanol was significantly less nephrotoxic than ioxaglate, an ionic, dimeric LOCM. (The RECOVER Trial; [http://clinicaltrials.gov; NCT00247325](http://clinicaltrials.gov; NCT00247325)) (J Am Coll Cardiol 2006;48:924–30) © 2006 by the American College of Cardiology Foundation
hypothesis that contrast hyperosmolality contributes to the nephrotoxicity of contrast media. Because LOCMs are hyperosmolar to plasma, it has been suggested that iso-osmolar contrast media (IOCM), which are iso-osmolar to plasma, may be even less nephrotoxic than LOCMs. Two prospective, randomized, controlled trials comparing the renal effects of the nonionic, dimeric, IOCM ioxaglate and the nonionic, monomeric, LOCM iohexol, one in patients undergoing renal and/or peripheral angiography and the other in patients undergoing coronary and/or aortofemoral angiography, have shown that iodixanol is significantly less nephrotoxic than the nonionic, monomeric LOCM iohexol (14,15). However, clinical studies are needed to compare the renal effects of iodixanol with those of other LOCMs, i.e., ionic and dimeric, to confirm that contrast hyperosmolality is the main cause of CIN rather than other physicochemical properties such as viscosity or ionicity.

In this article, we report the results of a randomized, prospective, controlled, single-center trial that compared the nephrotoxicity of the nonionic, dimeric, IOCM iodixanol with the ionic, dimeric, LOCM ioxaglate in patients with renal insufficiency undergoing coronary angiography with or without PCI.

METHODS AND PATIENTS

Methods. The RECOVER (Renal Toxicity Evaluation and Comparison Between Visipaque and Hexabrix in Patients With Renal Insufficiency Undergoing Coronary Angiography) study compared the nephrotoxicity of iodixanol and ioxaglate used as contrast media in patients undergoing coronary angiography with or without PCI. Both patients and investigators were blinded regarding study group assignment. Patients were randomized by the permuted block randomization method to receive iodixanol or ioxaglate. Coronary angiography was performed according to standard protocols for our center using the radial or femoral approach. Patients received intravenous half-isotonic saline at a rate of 1 ml/kg/h at least 8 h before and after coronary angiography. The SCr was measured in the morning on the day before coronary angiography (day -1) before the start of pre-hydration and on days 1 and 2 after the procedure. The highest SCr on day 1 or day 2 was used to calculate the change in SCr. All SCr levels were determined in a blinded fashion by laboratory personnel who measured it by autoanalyzer in the Department of Laboratory Medicine in Seoul National University Hospital. The Cockcroft-Gault formula was used to calculate creatinine clearance (CrCl) (16).

The primary end point was the incidence of CIN, defined as a relative increase in SCr from baseline of ≥25% or an absolute increase of ≥0.5 mg/dl (≥44.2 µmol/l) during days 1 and 2. Secondary end points included the proportion of patients showing an increase in SCr of ≥0.5 mg/dl (≥44.2 µmol/l), the proportion with a ≥1.0 mg/dl (≥88.4 µmol/l) increase in SCr, and the mean peak increase in SCr. In addition, data were subanalyzed according to the presence of severe renal impairment (defined as baseline CrCl <30 ml/min), concomitant diabetes, the use of ≥140 ml contrast media, low left ventricular systolic function (left ventricular ejection fraction [LVEF] by echocardiography <40%), and patient age (<75 vs. ≥75 years). Risk factors for CIN were determined.

Adverse events occurring during hospitalization and during 1 month after hospitalization were recorded. A compositive safety end point (death, myocardial infarction, revascularization, cerebral infarction, dialysis after contrast procedure) was analyzed.

Patients. Patients referred to the Cardiovascular Center at Seoul National University Hospital, Seoul, Korea, for coronary angiography with or without PCI were screened from January 2004 through December 2004. Patients age ≥19 years with CrCl rates ≥60 ml/min (≥1 ml/s) using the Cockcroft-Gault formula were considered to be eligible (16). Exclusion criteria were pregnancy, lactation, having received contrast media within 7 days of study entry, emergent coronary angiography, acute renal failure, end-stage renal disease requiring dialysis, history of hypersensitivity reaction to contrast media, cardiogenic shock, pulmonary edema, multiple myeloma, mechanical ventilation, parenteral use of diuretics, use of N-acetylcysteine, and use of metformin or nonsteroidal anti-inflammatory drugs within 48 h of the procedure. The protocol was approved by the Institutional Review Board at our institution. All patients provided informed, written consent.

Statistical analysis. For calculation of the sample size, a 20% incidence of CIN for the ioxaglate group and an 8% incidence for the iodixanol group (corresponding to a 60% difference between the 2 groups) were assumed (17–19). Using this assumption, a sample size of 128 patients per group would permit a 2-sided significance level of 5% and 80% power. To allow for the possibility of patients lost during follow-up, incomplete data collection, and protocol violations, the planned sample size was 150 patients in each group.

Data were analyzed from the per-protocol population. All data are presented as percentages or as mean ± standard deviation. Comparisons of baseline data were performed using the chi-square test or Fisher exact test (categorical variables) and the Student t test (continuous variables).
Univariate and multivariate logistic regression analysis were performed using all potentially relevant variables. All p values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS software version 13.0 (SPSS Inc., Chicago, Illinois).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Patient demographics and disposition. Between January 2004 and December 2004, of a total of 2,474 consecutive patients screened, 300 were randomized to receive iodixanol (n = 151) or ioxaglate (n = 149). After exclusions because of protocol violations, incomplete laboratory test results, and insufficient follow-up, 140 patients receiving ioxaglate and 135 patients receiving iodixanol were included in the per-protocol analysis (Fig. 1). Demographic and baseline data are provided in Table 1. The patient groups did not differ significantly with the exception of age.

Primary end point—the incidence of CIN. Eleven patients in the iodixanol group (7.9%) and 23 patients in the ioxaglate group (17.0%) had an increase in SCr from baseline of ≥25% or ≥0.5 mg/dl (≥44.2 μmol/l) within 2 days of contrast media administration (p = 0.021) (Fig. 2). The odds ratio (OR) for CIN according to this definition for the iodixanol group (using the ioxaglate group data as reference) was 0.415 (95% confidence interval [CI] 0.194 to 0.889).

The incidence of increases in SCr from baseline of ≥0.5 mg/dl (≥44.2 μmol/l) and ≥1.0 mg/dl (≥88.4 μmol/l) were also analyzed. Fewer patients in the iodixanol group (5; 3.6%) showed an increase of ≥0.5 mg/dl (≥44.2 μmol/l) compared with the ioxaglate group (12; 8.9%), but this difference did not reach statistical significance (p = 0.067). Two patients in the iodixanol group (1.4%) and 6 in the ioxaglate group (4.4%) had an increase in SCr from baseline of ≥1.0 mg/dl (≥88.4 μmol/l), but the difference was not significant (p = 0.167).

Subgroup analyses. The incidence of CIN among patients with severe renal impairment was significantly lower for
patients receiving iodixanol (2 of 16 patients; 12.5%) compared with that for patients receiving ioxaglate (8 of 15 patients; 53.3%) (p = 0.023). Similarly, the incidence of CIN was significantly lower for diabetic patients in the iodixanol group (5 of 48 patients; 10.4%) compared with that for diabetic patients in the ioxaglate group (18 of 105 patients; 17.1%) (p = 0.041). In patients who received ≥140 ml of contrast medium, the incidence of CIN in the iodixanol group (8 of 82 patients; 9.8%) was significantly lower than in the ioxaglate group (19 of 89 patients; 21.3%) (p = 0.038). In patients with mildly depressed or preserved LVEF (EF ≥40%), CIN was significantly less frequent with iodixanol (6 of 115 patients; 5.2%) compared with ioxaglate (17 of 113 patients; 15.0%) (p = 0.014), but in patients with moderately or severely depressed LVEF (EF <40%), the frequency of CIN did not differ between iodixanol (5 of 21 patients; 23.8%) and ioxaglate (5 of 20 patients; 25.0%) (p = 1.0). Finally, in patients <75 years, the incidence of CIN was significantly lower in iodixanol patients (9 of 115 patients; 7.8%) compared with ioxaglate patients (18 of 105 patients; 17.1%) (p = 0.035). In patients ≥75 years, the incidence of CIN was not different between the contrast media (Table 2).

### Risk factors for CIN.

Univariate analysis was performed to identify baseline and procedural risk factors for development of CIN. Baseline risk factors associated with CIN in the study patients included hypertension (defined as systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg) (p = 0.008), diabetes (p = 0.024), dyslipidemia (defined as total cholesterol level ≥240 mg/dl or patients who have taken statins) (p = 0.028), basal SCr (continuous variable) (p = 0.007), and left ventricular systolic function (continuous variable) (p = 0.002). Age was not a risk factor by univariate analysis. Procedural variables associated with CIN were dose of contrast media used (continuous variable) (p = 0.048) and use of ioxaglate (p = 0.024).

Multivariate analysis identified 3 risk factors for the development of CIN in study patients: use of ioxaglate (OR 2.65; 95% CI 1.11 to 6.33; p = 0.028), baseline SCr, mg/dl

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**Table 1.** Clinical, Biochemical, and Procedural Characteristics of Patients in the Per-Protocol Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Iodixanol (n = 140)</th>
<th>Ioxaglate (n = 135)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs*</td>
<td>66.1 ± 8.6</td>
<td>68.7 ± 7.5</td>
<td>0.010</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>79/61</td>
<td>75/60</td>
<td>0.884</td>
</tr>
<tr>
<td>Weight, kg*</td>
<td>59.70 ± 9.35</td>
<td>59.38 ± 9.53</td>
<td>0.778</td>
</tr>
<tr>
<td>BMI, kg/m²**</td>
<td>23.45 ± 2.90</td>
<td>23.40 ± 3.00</td>
<td>0.899</td>
</tr>
<tr>
<td>LVEF, %*</td>
<td>55.2 ± 13.2</td>
<td>54.4 ± 13.1</td>
<td>0.619</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>48 (34.3)</td>
<td>49 (36.3)</td>
<td>0.727</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>73 (52.1)</td>
<td>77 (57.0)</td>
<td>0.415</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>40 (28.6)</td>
<td>44 (32.6)</td>
<td>0.469</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>18 (12.9)</td>
<td>14 (10.4)</td>
<td>0.520</td>
</tr>
</tbody>
</table>

*Values are mean ± standard deviation. †All p values derived from the chi-square test. ‡To convert values for serum creatinine to micromoles per liter, multiply by 88.4. To convert values for CrCl to ml/s, multiply by 0.01667.

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**Figure 2.** Incidence of contrast-induced nephropathy according to 3 definitions for patients receiving iodixanol and ioxaglate as contrast media for coronary angiography. SCr = serum creatinine.
(OR 2.0; 95% CI 1.04 to 3.85; p = 0.038), and LVEF, % (OR 0.97; 95% CI 0.94 to 0.99; p = 0.019).

**Absolute peak increase in SCR and incidence of acute renal failure requiring dialysis.** For patients receiving iodixanol, mean SCR increased from the baseline level of 1.38 ± 0.56 mg/dl (121.9 ± 49.5 μmol/l) to a peak of 1.40 ± 0.63 mg/dl (123.8 ± 55.7 μmol/l) within 2 days of the contrast procedure; this change was not significant (p = 0.288). However, for patients receiving ioxaglate, mean SCR increased significantly from a baseline level of 1.30 ± 0.50 mg/dl (114.9 ± 44.2 μmol/l) to a peak of 1.44 ± 0.79 mg/dl (127.3 ± 69.8 μmol/l) (p = 0.001) (Fig. 3). The iodixanol group showed a significantly smaller mean increase in SCR compared with the ioxaglate group (0.26 ± 0.26 vs. 0.144 ± 0.50 mg/dl; p = 0.015). The overall peak SCR was observed on day 1 in 42.2%, on day 2 in 34.9%, and equal value on both days in 22.9% of all patients. In patients with CIN, the peak SCR level was observed mainly on day 2 (22 of 34 patients; 64.7%), but in patients in whom CIN did not occur, it was observed mainly on day 1 (106 of 241 patients; 44.0%).

Two patients developed acute renal failure requiring hemodialysis: 1 patient in the iodixanol group and 1 in the ioxaglate group. Both patients returned to their basal levels of renal function before hospital discharge, but several months later required hemodialysis, which was unrelated to on-study coronary angiography.

**Composite safety end point.** There was no difference between the groups in terms of the composite safety end point (death, myocardial infarction, revascularization, cerebral infarction, dialysis after contrast procedure) in the iodixanol group (3 of 140 patients; 2.1%) and the ioxaglate group (3 of 135 patients; 2.2%).

**DISCUSSION**

To our knowledge this is the first study to compare the nephrotoxicity of iodixanol, a nonionic dimeric IOMC, with ioxaglate, an ionic dimeric LOCM. We found that in patients with renal impairment, iodixanol was associated with a significantly lower incidence of CIN than ioxaglate. The incidence of CIN was also significantly lower with iodixanol in those patients with severe renal impairment (baseline CrCl <30 ml/min), those with concomitant diabetes, those who received ≥140 ml of contrast, those with LVEF ≥40%, and age <75 years. In multivariate analysis, use of ioxaglate was an independent risk factor for CIN.

A large body of clinical data has shown that LOCMs are associated with a lower incidence of CIN compared with HOCMs in patients with renal impairment (7,11–13). The incidence of CIN associated with iodixanol in high-risk patients has previously been shown to be significantly lower than that with iohexol, a nonionic, monomeric LOCM in 2 studies. Chalmers and Jackson (14) conducted a prospective, single-center, randomized, unblinded trial in which 124 patients with SCR >1.7 mg/dl, 34 of whom had diabetes, received iodixanol and iohexol during renal and/or peripheral angiography. A significantly smaller proportion of patients receiving iodixanol had an increase in SCR >10% compared with those receiving iohexol (15% vs. 31%; p < 0.05), and a lower proportion of patients in the iodixanol group had a >25% increase in SCR than those in the iohexol group (3.7% vs. 10%; p = NS) (14). Aspelin et al. (15) confirmed these results in a prospective, multicenter, double-blind trial (NEPHRIC [Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media]) comparing the nephrotoxicity of iodixanol and iohexol in 129 diabetic patients with SCR between 1.5 (132.6 μmol/l) and 3.5 mg/dl (309.4 μmol/l) undergoing coronary or aortofemoral angiography. The incidence of CIN (defined as a ≥0.5 mg/dl [44.2 μmol/l] increase in SCR) was significantly lower in the iodixanol group compared with the iohexol group (3% vs. 26%; p = 0.002) (15).

Like iohexol, ioxaglate is a LOCM; however, although iohexol is nonionic and monomeric, ioxaglate is ionic and dimeric. The finding that iodixanol is less nephrotoxic than...
Osmolality is a useful characteristic for classifying iodinated contrast media. The older, high-osmolar agents such as diatrizoate are very hyperosmolar (~7 times that of blood). The so-called LOCM are still considerably hyperosmolar (~2 to 3 times that of blood) (17), and iodixanol is the only iodinated contrast agent not hyperosmolar to blood. Experimental studies investigating the role of osmolality in the pathogenesis of CIN have produced conflicting results (20–22), but as noted above, evidence from prospective, randomized clinical trials suggests an association between CIN and contrast osmolality rather than between CIN and contrast viscosity, ionicity, or chemotoxicity. To date, there is no high-quality clinical evidence from prospective, randomized, controlled clinical trials to support the notion that contrast viscosity causes CIN.

In our study the patients receiving ioxaglate were 2.5 years older on average than the patients receiving iodixanol, and the difference was significant (p = 0.010). In some studies, advanced age has been reported to increase the risk of CIN (8), but the difference between the iodixanol and ioxaglate groups is likely to be too small to be relevant to the greater incidence of CIN in the ioxaglate group. Moreover, in the univariate and multivariate analyses, age was not a greater incidence of CIN in the ioxaglate group. Moreover, the iodixanol and ioxaglate groups is likely to be too small to be relevant to the potential for reduced health care costs in populations that traditionally have been associated with longer hospital stays and greater use of health care resources (25,26).

In patients given greater doses of contrast media, iodixanol was also less likely to cause CIN than ioxaglate. In the subgroup of patients with more severely depressed LVEF, we could not detect a difference in CIN between the 2 contrast media (23.8% vs. 25%, p = 1.0), but in the group of mildly depressed or preserved LVEF (~40%), iodixanol media might be more effective in preventing CIN than the half-isotonic saline used in our study (23).

In the subgroups of patients with more severe renal insufficiency and with diabetes, iodixanol was less likely to cause CIN than ioxaglate. Specifically, in patients with severe renal impairment (CrCl <30 ml/min), ioxaglate was associated with a significantly higher (4 times) incidence of CIN than iodixanol (p = 0.023). In diabetic patients with renal dysfunction (CrCl <60 ml/min), the incidence of CIN was also significantly higher (2.5 times) with ioxaglate than iodixanol (p = 0.041) (Table 2). Based on these findings, iodixanol seems to offer greater clinical benefit than ioxaglate in renally compromised, sicker populations for whom the risk of CIN and its associated morbidity and mortality are known to be highest (3,6,8,9,24). This supports and extends the findings of the NEPHRIC study, which also showed that iodixanol led to a greater reduction in the incidence of CIN compared with the nonionic LOCM iohexol in a high-risk population of patients with both diabetes and renal impairment (15). With the aging population and the incidence of diabetes increasing, older and sicker patients with serious renal and cardiovascular comorbidities now comprise a large proportion of those undergoing coronary angiography. Given this trend, the apparent clinical benefit shown for iodixanol versus ioxaglate here has important implications not only in terms of the potential for improved patient outcomes but also in terms of the potential for reduced health care costs in populations that traditionally have been associated with longer hospital stays and greater use of health care resources (25,26).

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had a preventive effect (5.2% vs. 15%, p = 0.014). This result might suggest that in patients with severely depressed LVEF, the left ventricular systolic function itself plays a more significant role than the type of contrast media in the occurrence of CIN (Table 2). Although we observed a lower incidence of CIN with ioxaglate than with ioxaglate in patients aged <75 years, the fact that there is only a trend in favor of ioxaglate in patients ≥75 years is probably attributable to the small sample size in this patient subset.

In the present study, we did not observe any significant difference between ioxaglate and ioxaglate in a composite end point of several serious adverse events (death, myocardial infarction, revascularization, cerebral infarction, dialysis after contrast procedure) during a 30-day follow-up. This study was not sufficiently powered to fully evaluate the incidence of serious adverse events, and the follow-up period of 30 days does not provide data on long-term sequelae after iodixanol and ioxaglate administration. Ionic contrast media such as ioxaglate have greater anticoagulant properties than nonionic contrast media such as iodixanol in vivo (27,28). To date, however, this difference has not been linked to a greater incidence of major cardiovascular adverse events with iodoxanol, relative to ioxaglate, in clinical trials involving both high-risk (29) or lower-risk (30) cardiac populations.

The finding of reduced nephrotoxicity with iodixanol in this and other studies is clinically important because of the association of CIN with longer hospitalization, delayed treatments and procedures, and greater short-term and long-term morbidity and mortality. Data from large, long-term trials are needed to confirm a correlation between iodixanol and ioxaglate administration. Ionic contrast media such as ioxaglate have greater anticoagulant properties than nonionic contrast media such as iodixanol in vivo (27,28). To date, however, this difference has not been linked to a greater incidence of major cardiovascular adverse events with iodixanol, relative to ioxaglate, in clinical trials involving both high-risk (29) or lower-risk (30) cardiac populations.

In conclusion, iodixanol, a nonionic, dimeric IOCM, was associated with a significantly lower incidence of CIN than ioxaglate, an ionic, dimeric IOCM in patients with renal impairment as well as a subgroup of diabetes or patients receiving a high dose of contrast media.

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