Nephrotoxicity of iodixanol versus ioversol in patients with chronic kidney disease: The Visipaque Angiography/Interventions with Laboratory Outcomes in Renal Insufficiency (VALOR) Trial

Michael R. Rudnick, MD, FACP, FASN, a Charles Davidson, MD, FACC, b Warren Laskey, MD, FACC, c J. Lawrence Stafford, MD, FACC, d and Paul F. Sherwin, MD, PhD e For the VALOR Trial Investigators f
Philadelphia, PA, Chicago, IL; Albuquerque, NM; Baltimore, MD; and Princeton, NJ

Background Iso-osmolar contrast medium iodixanol has been reported to be less nephrotoxic than selected low-osmolar contrast media (LOCM) in chronic kidney disease (CKD) patients with diabetes mellitus. This study compared the nephrotoxicity of iodixanol and the LOCM ioversol in CKD patients undergoing coronary angiography.

Methods This is a prospective double-blind trial in 337 patients with stable CKD who were randomly assigned to receive the iso-osmolar contrast medium iodixanol or the LOCM ioversol. The co-primary end points were the mean peak percentage change (MPPC) in baseline serum creatinine and the incidence of contrast-induced nephropathy (rise of >0.5 mg/dL in baseline serum creatinine within 72 hours postcontrast) for the 2 contrast media in the 72-hour period after contrast administration. Prespecified analyses included stratification on diabetic state and the use of N-acetylcysteine.

Results In the 299 patients with complete post–contrast media creatinine data, the incidence of contrast-induced nephropathy was 21.8% in the iodixanol subjects and 23.8% in the ioversol subjects (P = .78). For all patients, the MPPC was 14.7% with iodixanol and 20.0% with ioversol (P = .06), whereas in the subset of diabetic patients, this value was significantly lower in the iodixanol (12.9%) compared with the ioversol subjects (22.4%, P = .01).

Conclusions Overall, the nephrotoxicity associated with iodixanol was not significantly different from that observed with ioversol in CKD patients undergoing coronary angiography, although in diabetic patients, MPPC was significantly lower in the iodixanol group. (Am Heart J 2008;0:1-7.)

Intravascular administration of iodinated contrast media (CM) has long been recognized as one of the most frequent causes of hospital-acquired acute kidney injury.1 The risk for contrast-induced nephropathy (CIN) is significantly increased in patients with chronic kidney disease (CKD), especially if diabetes mellitus (DM) coexists.2 The increasing use of intravascular CM3 and the high prevalence of significant CKD in the United States4 suggest that the incidence of CIN will continue to rise.

The risk for CIN also depends on the type of CM administered. Modern-day CM are benzoic acid derivatives containing 3 iodine atoms per benzene ring.5 Initial formulations were ionic, resulting in high osmolalities (approximately 1,500 mOsm/kg water) and their classification as high-osmolar CM (HOCM).5 In the 1980s, CM formulations were introduced in which the iodine-containing benzene ring was nonionic, resulting in a marked reduction in osmolality (approximately 600-700 mOsm/kg water).5 These second-generation CM are classified as low-osmolar CM (LOCM) and are the principal CM used for intravascular radiological studies. Experimental and clinical studies in high-risk patients demonstrated that LOCM were associated with reduced nephrotoxicity compared with HOCM.2,6 Although the specific physical and chemical properties of LOCM that were responsible for the reduction in nephrotoxicity have not been definitively determined, the reduction in osmolality may be responsible and is consistent with proposed mechanisms for contrast-induced renal injury.7
Recently, a third generation of CM was introduced in which 2 iodine-containing benzene rings are linked in a dimer, resulting in a further reduction in osmolality to 280 mOsm/kg water; these have been referred to in the medical literature as iso-osmolar contrast agents (IOCM). Currently, iodixanol is the only IOCM approved for use in the United States. In view of the reduction of nephrotoxicity with LOCM compared with HOCM, it is not surprising that clinical trials were conducted to determine if IOCM conferred a further reduction in nephrotoxicity compared with LOCM. In this regard, in 2003, Aspelin et al reported a significant reduction in CIN with iodixanol compared with the LOCM iohexol in patients with CKD and DM.

The purpose of the current trial was to determine if there was a more favorable impact on renal function with the IOCM iodixanol versus the LOCM ioversol in patients with CKD both with and without DM undergoing cardiac angiography.

Materials and methods

Organization

The Visipaque Angiography/Interventions with Laboratory Outcomes in Renal Insufficiency (VALOR) trial enrolled patients from 39 participating centers across the United States and Canada. The original protocol and its amendments were approved by the respective institutional review boards at each participating center in accord with the principles of the Declaration of Helsinki, and all patients gave informed consent. The authors have had full access to the data, take responsibility for the data's integrity, and agree to the article as written.

Study population

Enrollment began in November 2001 and ended in January 2004. Patients >18 years of age with CKD (≥1.7 mg/dL for men and ≥1.5 mg/dL for women) who were referred for coronary angiography with or without percutaneous coronary intervention (PCI) and requiring at least 30 mL of CM were eligible. Exclusion criteria included acute cause(s) for the elevated serum creatinine (Scr) value or a Scr value unstable by >0.5 mg/dL within 10 days of study entry; hemodynamic instability pre-study (systolic blood pressure <90 mm Hg within 72 hours before contrast administration); pregnancy; lactation; intravascular administration of iodinated CM within 7 days before study entry; a requirement for additional intravascular iodinated CM for any purpose between 8 and 72 hours after initial CM administration; the scheduling of a major surgical intervention within 72 hours after the study procedure; the administration of theophylline, fenoldopam, or mannitol within 7 days before or 72 hours after contrast administration; the initiation, discontinuation, or change in dose of any of the following—trimethoprim, cimetidine, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker—within 72 hours before study entry; end-stage renal disease requiring dialysis or organ transplantation; initiation of nephrotoxic agents, or nonsteroidal anti-inflammatory drugs within 72 hours of study entry; current use of metformin; severe liver or hematologic disease; severe heart failure (defined as requiring therapy with intravenous diuretics, inotropes, and/or vasodilators); or a history of serious reaction to intravascular iodinated CM. Subjects with acute myocardial infarction requiring urgent coronary angiography were not excluded from participation.

Study protocol

This was a prospective, randomized, double-blind study of the nephrotoxic effects of the IOCM iodixanol (Visipaque, Amersham Health, 320 mg-I/mL, osmolality 290 mOsm/kg water) compared with the LOCM ioversol (Optiray, Mallinckrodt Inc, 320 mg-I/mL, osmolality 702 mOsm/kg water) in subjects with CKD undergoing coronary angiography with or without PCI.

The initial protocol randomized CKD patients to receive either iodixanol or ioversol and excluded the use of N-acetylcysteine (NAC); 3 patients were enrolled under this version. Shortly after study initiation, NAC was reported to protect against nephrotoxicity, limiting acceptance of the original protocol by investigators and institutional review boards. In response, the protocol was amended (May 2002) to randomize subjects to iodixanol alone, iodixanol with NAC, or ioversol with NAC. After this amendment, it was observed that enrollment was difficult because many potential subjects had been pretreated with NAC before they could be evaluated for the study, making them ineligible. Forty-one patients were enrolled under this amendment. Given the logistic issues for timely enrollment, the appearance of reports that failed to demonstrate a renoprotective effect of NAC, and the observation that participating centers either routinely did or did not use NAC, the protocol underwent its final amendment in January 2003 to randomize subjects 1:1 to iodixanol or ioversol and to allow NAC use at the physician’s discretion. Most of the subjects (n = 293, 87%) in this report were enrolled under the final protocol version.

Each patient was assigned 1 of the 2 contrast agents, with equal probability based on a computer-generated randomization schedule. To avoid bias, subjects and site personnel involved in subject recruitment, CM administration, safety evaluation, and end point determination were blinded as to the identity of the CM the subject received. Cardiac angiography with or without PCI was performed according to the standard procedure of each study site. Preprocedural and procedural medications were recorded, as were the details of the angiography including procedure performed and total contrast volume administered. Sodium chloride solution (0.9%) was infused intravenously at 125 mL/h for at least 2 hours before and at least 6 hours after CM administration (for patients with congestive heart failure, the infusion rate could be reduced to 50 mL/h). Oral fluid intake was encouraged ad libitum. Use of NAC was left to the investigator’s discretion. If NAC was to be used, the recommended dose was 1,200 mg orally 1 hour before and 4 hours after contrast administration.

Within 7 days before CM administration, demographic information, medical history, physical examination, and Scr measurement (at the local laboratory) were performed. Serum creatinine was measured at a central laboratory on samples taken just before contrast administration but after prehydration and 24, 48, and 72 hours after contrast administration. In subjects in whom Scr rose by ≥0.5 mg/dL, Scr was measured at
7 days post-CM administration and remeasured until the Scr was no longer ≥0.5 mg/dL above baseline or until 28 days had elapsed, whichever occurred first.

Statistical analysis

The 2 co-primary end points in this study were the mean peak percentage change (MPPC) from baseline in Scr for the 2 CM groups over the 72-hour period after CM administration (hypothesis 1) and the percentage of subjects in each CM group who experienced CIN defined as an increase in Scr from baseline of ≥0.5 mg/dL up to 72 hours post-contrast administration (hypothesis 2). Hypothesis 1 was tested using the usual 2-sample \( t \) test, and hypothesis 2 was tested using the usual \( \chi^2 \) test for equality of proportions. The protocol also specified that secondary analyses of the interactions of DM and NAC use with treatment arm would be performed.

Because the true effect (if any) of NAC on the CIN rate and the true rate of NAC use at the start of the study were unknown, an interim analysis, after 200 patients had been enrolled, was planned to test assumptions around NAC effect and NAC use and to allow sample size adjustment if needed. The initial sample size of 200 total patients was chosen based on the literature data available for MPPC in Scr and would provide 90% power of detecting a 5% difference between the ioversol and the iodixanol treatment groups if the common SD was 10%, or a 10% difference if the common SD was 20%. If both end point differences were shown to be statistically significant in the interim analysis, the study was to be terminated and the final data analysis performed. If a significant difference between contrast agents for one of the co-primary end points could not be demonstrated in the interim analysis, then an additional 300 subjects would be enrolled, with the anticipation that this would provide sufficient sample size with adequate power to fully test both hypotheses.

Study termination

After the blinded interim analysis, a significant increase in CIN was noted in the subjects who had received NAC compared with subjects who had not (NAC 25.7%, no NAC 14.3%, \( P = .04 \)) and the MPPC (NAC 18.9%, no NAC 17.5%, \( P = .02 \)). Because of this finding, the sponsor of the study suspended further subject enrollment and convened an external data review board to conduct a blinded review of the interim data. At the completion of its review of the interim data, the data review board was unable to demonstrate that patients at “higher risk” for CIN preferentially received NAC and recommended that the sponsor terminate the study and publish the interim results.

Results

Study flow

At study termination, 337 subjects (iodixanol \( n = 173 \), ioversol \( n = 164 \)) had been enrolled and received study medication (intention to treat [ITT] group) (Figure 1). Of this group, 3 subjects had no postprocedure Scr measurements and could not be included in the primary end point analyses for the ITT population. Of the 337 subjects who received study medication, 17 subjects in the iodixanol group and 21 subjects in the ioversol group did not have a complete set of Scr values for the 24-, 48-, and 72-hour collection points after CM administration; and as per the protocol, these 38 subjects were not included in the evaluable subjects. None of these patients demonstrated an increase in Scr of ≥0.5 mg/dL. The remaining 299 subjects (evaluable group) are the population evaluated for primary end points and co-factor associations, unless otherwise noted. There were 68 (iodixanol \( n = 34 \), ioversol \( n = 34 \)) subjects who had a ≥0.5 mg/dL increase in Scr.

### Table I. Clinical characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Iodixanol (n = 156)</th>
<th>Ioversol (n = 143)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>68.2%</td>
<td>73.8%</td>
<td>.28</td>
</tr>
<tr>
<td>Race (white)</td>
<td>76.9%</td>
<td>76.8%</td>
<td>.86</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>71.1 ± 9.9</td>
<td>72.6 ± 10.2</td>
<td>.22</td>
</tr>
<tr>
<td>Diabetes</td>
<td>52.0%</td>
<td>51.8%</td>
<td>.97</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>89.2 ± 21.4</td>
<td>90.2 ± 19.5</td>
<td>.66</td>
</tr>
<tr>
<td>Mean body surface area</td>
<td>2.00 ± 0.2</td>
<td>2.02 ± 0.2</td>
<td>.38</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>145/75</td>
<td>149/75</td>
<td>.13</td>
</tr>
<tr>
<td>Baseline creatinine (mg/dL)</td>
<td>1.99 ± 0.6</td>
<td>1.92 ± 0.6</td>
<td>.27</td>
</tr>
<tr>
<td>Baseline GFR</td>
<td>36.5 ± 11.3</td>
<td>38.8 ± 11.1</td>
<td>.09</td>
</tr>
</tbody>
</table>

(\( \text{mL}/[\text{min} \times 1.73 \text{m}^2]\))^\(\text{a}\)

Concomitant medications

- Calcium-channel blockers: 37.8% vs 43.4%, \( P = .35 \)
- Diuretics: 74.4% vs 74.1%, \( P = 1.00 \)
- ACEIs/ARBs: 65.4% vs 69.9%, \( P = .46 \)

| Mean volume of contrast (mL)     | 118.4 ± 83.8        | 129.9 ± 80.8       | .23   |
| Mean volume of contrast (mL/kg body weight) | 1.43 ± 1.2          | 1.51 ± 1.1         | .55   |
| Mean total IV hydration (mL)†    | 1311 ± 686          | 1420 ± 765         | .20   |
| NAC use                          | 70.5%               | 76.2%              | .86   |
| NAC total dose (mg)              | 2651 ± 2591         | 2787 ± 3505        | .74   |

GFR, Glomerular filtration rate; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; IV, intravenous.

†Total intravenous hydration given pre-, during, and postangiography.
Clinical characteristics

As presented in Table I, there were no statistically significant differences in clinical characteristics between the evaluable iodixanol and ioversol subjects.

Renal outcome data

Primary end points: MPPC and CIN. The MPPC from baseline in Scr during the 72 hours after contrast administration (Figure 2) was not significantly lower in the iodixanol compared with the ioversol group (14.7% ± 19.5% vs 20.0% ± 17.8%, respectively) ($P = .06$). The mean difference and 95% CI for the difference in MPPC (ioversol vs iodixanol) was 5.33% and CI $-0.10\%$ to $10.76\%$. The incidences of CIN were 21.8% ($n = 34/156$) in the iodixanol group compared with 23.8% ($n = 34/143$) in the ioversol group ($P = .78$) (Figure 3). The CIN rate difference and 95% CI for the difference in CIN (ioversol vs iodixanol) was 1.98% and CI $-7.5\%$ to $11.5\%$. Analysis of the ITT population gave similar CIN results: iodixanol 19.9% ($34/171$) and ioversol 20.9% ($34/163$) ($P = .89$). Calculation of the MPPC in baseline Scr for the ITT population also yielded similar results: iodixanol 14.3% ± 18.8% and ioversol 18.3% ± 26.7% ($P = .11$).

For ioversol patients, 38%, 44%, and 18% of the CIN patients developed their CIN by the end of day 1, 2, and 3, respectively; for iodixanol, the corresponding incidences were 21%, 59%, and 21%, respectively.

Association of CIN rates and MPPC with DM alone, NAC alone, and NAC and DM combined. Prespecified secondary analyses were performed on the effects of DM on the MPPC in Scr (Figure 2) and the incidence of CIN (Figure 3). In subjects with DM, the MPPC was significantly lower in the iodixanol group versus the ioversol group (12.9% ± 16.3% vs 22.4% ± 17.8%, $P = .01$). For the entire population regardless of CM administered, the incidence of CIN was 21.4% ($n = 31/145$) in subjects without DM and 24.0% ($n = 37/154$) in subjects with DM ($P = .68$). In the subgroup with DM, the incidences of CIN were 21.9% in the iodixanol group compared with 26.4% in the ioversol group (mean difference 4.4%, 95% CI $-18.3\%$ to $9.4\%$) (Figure 3).

In iodixanol and ioversol subjects who did not receive NAC, the CIN incidence was 11.1% ($n = 5/45$) and 18.8% ($n = 6/32$), respectively ($P = .51$). In iodixanol and ioversol subjects who did receive NAC, the CIN incidence was 26.1% ($n = 29/111$) and 25.2% ($n = 28/111$), respectively ($P = 1.00$). Table II summarizes the combined interaction of DM and NAC on the incidence of CIN for each of the CM groups. There were no significant differences between the CM groups for any of the combined interactions.
Discussion

Current theories of CIN pathogenesis have primarily focused on disturbances in renal hemodynamics resulting in hypoxic injury to the kidney and direct cellular toxicity due to CM.\(^7\)\(^8\) It is postulated that, in addition to contrast-induced reductions in blood flow to the outer medulla, the hyperosmolality of CM may further worsen hypoxic injury by inducing a solute diuresis that in turn results in increased solute transport in the thick ascending limb of the Henle loop, a process requiring oxygen utilization.\(^15\)

Based upon these experimental observations and earlier clinical observations that demonstrate reduced CIN with LOCM compared with HOCM,\(^2\)\(^6\) the introduction of IOCM was not surprisingly followed by clinical studies designed to evaluate whether the incidence of CIN could be further reduced with CM that are iso-osmolar. These initial clinical trials supported the hypothesis that further reductions in CM osmolality were associated with a further reduction in CIN compared with LOCM.\(^8\)\(^16\)\(^17\) In the multicentered NEPHRIC trial, 135 patients with CKD and DM undergoing coronary or aortofemoral angiography were prospectively randomized to receive either ioxidanol or iohexol.\(^8\) The incidence of CIN (a rise in Scr of ≥0.5 mg/dL) was 3% in the ioxidanol group and 26% in the iohexol group (\(P = .002\)). In the RECOVER study, the incidence of CIN was significantly lower with ioxidanol (7.9%) compared with the LOCM ioxaglate (17.0%, \(P = .02\)) in 300 patients with a baseline creatinine clearance \(\leq 60 \text{ mL/min} \) who underwent coronary angiography.\(^17\) In contrast, other recent studies have not demonstrated a reduction in nephrotoxicity with ioxidanol compared with an LOCM. Barrett et al\(^16\) randomized 166 patients with CKD to ioxidanol or the LOCM iopamidol intravenously administered during computerized tomography. No significant difference in CIN (≥0.5-mg/dL change in Scr) was seen between the 2 contrast groups, possibly because of the intravenous route of administration compared with the intraarterial route in the other studies. In another recent study, Solomon et al\(^19\) (CARE study) compared the nephrotoxicities between iodoxanol and the LOCM iopamidol in 414 patients with CKD undergoing coronary angiography. The incidence of CIN (≥0.5 mg/dL rise in Scr) was similar in patients who received either iodoxanol (6.7%) or iopamidol (4.4%, \(P = .39\)). The question of reduced nephrotoxicity with IOCM compared with LOCM is further amplified in 2 other recent publications. In a systematic review of prospective, randomized, controlled trials in which the CIN incidence in high-risk patients could be determined, Solomon\(^20\) concluded that the incidence of CIN was similar between iodoxanol and the LOCM iopamidol. A different conclusion was reached by McCullough et al\(^21\) who performed a meta-analysis of prospective, randomized, controlled trials comparing iodoxanol to a pooled group of different LOCM. In this study, iodoxanol was associated with smaller rises in Scr and lower incidences of CIN than LOCM, especially in patients with CKD or CKD plus DM.

There are no prospective randomized trials directly comparing the nephrotoxicity of specific LOCM to each other in high-risk patients. Thus, well-designed, double-blinded, randomized, controlled clinical trials comparing iodoxanol to a “specific” LOCM are necessary to clarify possible differences in nephrotoxicity between this IOCM and a specific LOCM. It was for this purpose that we undertook a large, prospective, randomized, double-blind clinical trial to compare the nephrotoxicity of the IOCM iodoxanol to the LOCM ioversol in patients with CKD undergoing cardiac angiography. The results presented herein are based on the 299 subjects who entered the trial before termination and fulfilled all the requirements of the protocol. Thus, VALOR qualifies as one of the largest prospective randomized trials performed to date comparing the IOCM iodoxanol to a specific LOCM in patients with CKD.

The evaluation of the relative nephrotoxicity of these 2 CM in our trial was based on co-primary end points determined during the 72-hour period after contrast administration: the MPPC from baseline in Scr and the incidence of CIN. Although CIN has been traditionally used as an end point in all studies assessing contrast nephrotoxicity, the MPPC has also been increasingly used as an end point in more recent studies of contrast nephrotoxicity.\(^8\)\(^17\)\(^19\)\(^21\) This end point assesses creatinine changes for the entire population and may provide a more sensitive index of a contrast’s nephrotoxicity than CIN alone. The clinical significance of a specific quantitative rise in the MPPC as well as statistically significant differences in MPPC in Scr between contrast agents remains unknown at the present time but is consistent with an adverse alteration in renal function.

In this study, we failed to observe the hypothesized difference between measures of nephrotoxicity associated with ioversol versus iodoxanol. Only for the highest-risk subgroup with diabetes and CKD, despite no significant difference between treatment groups in CIN incidence, was there a statistically significant difference in the MPPC favoring iodoxanol over ioversol.

There are several possible explanations for the failure to demonstrate a statistically significant difference in the incidence of CIN between iodoxanol and ioversol. The most obvious of these explanations is that there is no clinically significant difference in nephrotoxicity between iodoxanol and ioversol in the population tested. However, because of the unexpected termination of this trial and the observed incidences of CIN, the study was underpowered to detect the hypothesized differences outlined in the statistical design. Based on the observed incidence of CIN for ioversol at the interim analysis, a sample size of 1,502 subjects in each treatment group...
would have been necessary to test, at a 90% power, for a 5% absolute reduction in the CIN rate for ioxidan. The inclusion of CKD patients without DM probably reduced the overall risk of CIN; this in turn may have further obscured a true difference in CIN risk between the 2 groups, resulting in the need for a larger sample size. In support of the latter is the finding of a statistically significant difference in MPPC favoring ioxidan for subjects with diabetes. It remains unknown, if more patients with DM had been studied, whether the differences between ioxidan and ioversol would have reached statistical significance for this subgroup. However, our data do allow us to state that, for this subgroup, the 95% CI of the difference in CIN between ioversol and ioxidan rules out a difference between agents of >18.3% favoring ioxidan or a difference of >9.4% favoring ioversol.

The use of NAC in 74% of the subjects in this study may have also obscured a more striking difference in nephrotoxicity between ioxidan and ioversol in the absence of NAC. A recent uncontrolled retrospective study comparing ioxidan to the LOMC iobitrnidl in patients at low to moderate risk for contrast nephrotoxicity demonstrated a low incidence of CIN for both CM (ioxidan 2.7%, iobitrnidl 3.5%, P = not significant).22 The authors suggested that any nephrotoxic advantage of the IOCM in this study may have been lost because of an equalizing protective effect of NAC that was administered to all patients. The incidence of CIN in diabetic subjects in our study who did not receive NAC was less in the ioxidan arm (Table II), but the number of such subjects was very small, and differences between the 2 treatment arms were not statistically significant.

Study limitations

As discussed above, a primary limitation of this study was that the premature termination of the trial resulted in a sample size smaller than needed to achieve the prespecified power. The use of co-primary end points has a statistical cost in respect to what is a significant P value. This turned out not to be relevant in our study because no statistically significant differences in CIN incidences between the 2 CM were observed. The exclusion of subjects who did not have a complete set of post-CM creatinine values may have unknowingly excluded some cases of CIN occurring at the missed time points, although we estimate that this at most would omit 8 cases of CIN (equally distributed between the 2 treatment arms), which would not change our overall results. Another limitation of this trial was the use of a posthydration precontrast creatinine measurement as the baseline value. It is possible that some patients whose Scr rose by ≥0.5 mg/dL did so solely because of elimination of fluids that diluted the baseline creatinine value. The effect of this, if present, would be to overestimate the true incidence of CIN.

Conclusions

The VALOR trial was a randomized, prospective, double-blind comparison of nephrotoxic risk between the IOCM ioxidan and the LOCM ioversol in patients with CKD. There were no statistically significant differences in the incidence of CIN between the 2 contrast agents tested. Similar to other studies comparing CM nephrotoxicity, we also evaluated MPPC from the baseline Scr.8,17-19,21 A statistically significant difference between agents was observed only in the highest-risk subgroup of patients with DM. These differences in the MPPC are of unclear clinical significance but certainly consistent with a diminished risk of nephrotoxicity with ioxidan in diabetic patients with CKD.

We greatly appreciate the statistical support of Gary Stevens, PhD.

References


Appendix A. Investigators in the VALOR Study

Bottner R (Savannah, GA), Cambier P (Safety Harbor, FL), Clark V (Detroit, MI), Davidson C (Chicago, IL), DeGent G (Greensboro, NC), Douglas J (Atlanta, GA), Eways E (Mobile, AL), Farrell P (Jacksonville, FL), Fenes A (Dallas, TX), Fung A (Vancouver, British Columbia, Canada), Gellman J (Fort Lauderdale, FL), Hanks WE (Fresno, CA), Hillegas W (Birmingham, CA), Khosla S (Chicago, IL), Kingsley E (Annapolis, MD), LaMarche N (Neptune, NJ), Mann T (Raleigh, NC), Markarian M (Lansing, MI), McFalls E (Minneapolis, MN), McGeehin F (Wynnewood, PA), Moreyra A (New Brunswick, NJ), Nader R (Miami Beach, FL), O’Bryan J (Ft Meyers, FL), O’Meallie L (New Orleans, LA), Papadakos S (Flushing, NY), Piana R (Nashville, TN), Puidlo J (Jacksonville, FL), Rohrbeck S (High Point, NC), Rudnick M (Philadelphia, PA), Rusterholtz L (Clearwater, FL), Schaefer G (Chicago, IL), Shunk K (San Francisco, CA), Stafford J (Baltimore, MD), Tobis J (Los Angeles, CA), Vernace M (Doylestown, PA), Weinstein I (Orlando, FL), Williams D (Providence, RI).