The Relative Renal Safety of Iodixanol Compared With Low-Osmolar Contrast Media

We read the article by Reed et al. (1) from the July 2009 issue of JACC: Cardiovascular Interventions with great interest, and we applaud the authors for their thoughtful analysis. We are pleased to see that the results, although not reaching statistical significance, favored iodixanol. However, there are several points to consider when interpreting the data. We would welcome any response from the authors.

First, the meta-analysis excluded publications favoring isosmolar iodixanol that were available during the scope of the published data capture. These publications include Hardiek et al. (2) (iodixanol vs. iopamidol), Nie et al. (3) (iodixanol vs. iopromide), and the Hernandez et al. (4) European Society of Cardiology abstract (iodixanol vs. ioversol).

Second, the studies included in the analysis varied regarding important parameters (e.g., patient demographic data, definition of contrast-induced acute kidney injury [CI-AKI]). One important variation is in the post-dose serum creatinine (SCr) protocol employed in terms of numbers of measurements and their timing. For example, of the included studies collected only a single SCr measurement with sample timing over a wide period of time. Assuming that each patient's renal response to contrast media varies, these studies might not have obtained a true CI-AKI rate. These studies are: the CARE (Cardiac Angiography in Renally Impaired Patients) study (iodixanol vs. iodixanol; SCr measured sometime between 45 and 120 h) (5); the PREDICT (A randomized double-blind comparison of contrast-induced nephropathy after low- or isosmolar contrast agent exposure) study (iopamidol vs. iodixanol; SCr measured sometime between 45 and 120 h) (5); the IMPACT (Contrast-induced nephropathy in patients with chronic kidney disease undergoing computed tomography: Iomeron 400 versus Visipaque 320 Enhancement) study (iomeprol vs. iodixanol; SCr measure sometime between 48 and 72 h) (6); and the ACTIVE (Investigators in the Abdominal Computed Tomography: Iomeron 400 versus Visipaque 320 Enhancement) study (iomeprol vs. iodixanol; SCr measure sometime between 48 and 72 h) (7); the IMPACT (Contrast-induced nephropathy in patients with chronic kidney disease undergoing computed tomography: a double-blind comparison of iodixanol and iopamidol) study (iopamidol vs. iodixanol; SCr measure sometime between 42 and 72 h) (8).

To date, there are no CI-AKI studies statistically favoring a low-osmolar contrast agent that obtained a true CI-AKI rate through multiple fixed (timing standardized for all patients in the study) SCr collections.

Third, the IMPACT study (8) should be excluded from the meta-analysis. The IMPACT study was a combination of 2 separate studies, VIRPACT (Visipaque 320 and Isovue 370 in Patients Undergoing Computed Tomographic Angiography of the Liver) and INVICTA (Isovue 370 and Visipaque 320 in Patients Undergoing Computed Tomographic Angiography of the Lower Extremities). Neither study examined contrast-induced nephropathy (CIN) as the primary end point, contrary to the impression given by the article by Barrett et al. (8). The primary objective of INVICTA was to examine the image quality in patients undergoing peripheral vascular imaging with either iopamidol-370 or iodixanol-320. The primary objective of VIRPACT was to examine the image quality in patients undergoing liver multidetector computed tomography with either iopamidol-370 or iodixanol-320. Both studies included examination of CIN rates in their secondary objectives. The VIRPACT and INVICTA studies were combined to form IMPACT after patient recruitment for VIRPACT and INVICTA was stopped and study data had been collected.

It would be interesting to know the results had the analysis included Hardiek, Hernandez, and Nie. Additionally, it would be interesting to know the results of the analysis had it focused on trials that employed a fixed SCr post-dose sampling protocol for all patients, a protocol that might more accurately depict the true CI-AKI differences between comparators.

GE Healthcare is a strong advocate of good patient care and good clinical design. We hope this clarifies the importance of evaluating the quality of CIN publications to properly analyze and understand the issue of CI-AKI.

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Reply
We would like to thank Drs. Cantor and Lim for their interest in our work (1). We disagree with their interpretation that the results of our analysis favor iodixanol and believe that the correct interpretation of our study is that iodixanol may be superior to some low osmolar contrast media (LOCM), but there is no data to suggest its superiority to other LOCM.

The authors point out 3 publications not included in the meta-analysis. Of the 3 reports they mention, one (Nie et al. [2]) was published outside our pre-defined search window (1980 through November 30, 2008). Inclusion of the other 2 trials did change the summary statistic slightly, although the results remained nonsignificant (risk ratio [RR]: 0.74, 95% confidence interval [CI]: 0.53 to 1.02, p = 0.069, for heterogeneity = 0.03). Inclusion of all 3 trials shifts the results in favor of iodixanol compared with the pool of LOCM (RR: 0.70; 95% CI: 0.50 to 0.97; p = 0.03, for heterogeneity = 0.02). However, the comparison of iodixanol with various types of LOCM remains unchanged: iodixanol causes less contrast-induced acute kidney injury (CI-AKI) compared with ioxaglate (3 studies; RR: 0.58; 95% CI: 0.37 to 0.92; p = 0.02) and iohexol (2 studies; RR: 0.19; 95% CI: 0.07 to 0.56; p = 0.002) but has no relative difference in CI-AKI compared with iopromide (5 studies; RR: 0.731; 95% CI: 0.36 to 1.48; p = 0.38), iopamidol (4 studies; RR: 0.97; 95% CI: 0.58 to 1.58; p = 0.89), and ioversol (2 studies; RR: 0.62; 95% CI: 0.22 to 1.74; p = 0.37). This re-emphasizes the point that iodixanol has similar renal safety compared with some contrast media and may be safer with respect to renal toxicity when compared with other LOCM.

The authors also indicate that the included studies varied in demographic and clinical parameters. Indeed, this is a limitation of all meta-analyses, but to some extent this makes the results more generalizable. With regard to the concern that some randomized trials only checked serum creatinine a single time after 48 h, it is worth reiterating that serum creatinine tends to peak 48 to 72 h after contrast exposure. Although more frequent serum creatinine checks may result in a higher observed incidence of CI-AKI in both the iodixanol and the LOCM groups, it is not clear this would change the overall conclusion of each study.

Contrary to the letter authors’ suggestion, the IMPACT (IMpaired PAtients undergoing Computed Tomography) trial appropriately fulfilled the criteria for inclusion in our analysis (3). Further, as demonstrated by our influence analysis, the exclusion of a single trial would not change the overall result of the meta-analysis.

We share the letter authors’ advocacy for quality patient care and quality clinical design. Further investigative trials comparing specific contrast media would continue to illuminate the most optimal ways to minimize CI-AKI. In light of conflicting data and ongoing debate, the proposed superior safety of iodixanol compared with all types of LOCM is less well established than when the 2007 American College of Cardiology/American Heart Association guidelines provided a Class IA recommendation for its use in the setting of unstable angina or non–ST-segment elevation myocardial infarction and renal insufficiency (4).

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