Rate of major adverse renal or cardiac events with iohexol compared to other low osmolar contrast media during interventional cardiovascular procedures

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Funding Information
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Abstract
Objective: This study assessed the rate of major adverse renal or cardiac events (MARCE) when iohexol is used during interventional cardiovascular procedures compared to other low osmolar contrast media (LOCMs).

Background: Interventional cardiovascular procedures are often essential for diagnosis and treatment, the risk of MARCE should be considered.

Methods: Data were derived from the Premier Hospital Database January 1, 2010 through September 30, 2015. Patient encounters with an inpatient primary interventional cardiovascular procedure with a single LOCM (iohexol, ioversol, ioxilan, ioxaglate, or iopamidol) were included. The primary outcome was a composite endpoint of MARCE, which included: renal failure with dialysis, acute kidney injury (AKI) with or without dialysis, contrast induced AKI, acute myocardial infarction, angina, stent occlusion/thrombosis, stroke, transient ischemic attack, or death. Multivariable regression analysis was performed using the hospital fixed-effects specification to assess the relationship between MARCE and iohexol compared to other LOCMs, while controlling for patient demographics, comorbid conditions and reason for hospitalization. As a sensitivity analysis, direct comparisons of iohexol were made to other LOCMs.

Results: A total of 458,091 inpatient encounters met inclusion criteria of which 26% used iohexol and 74% used other LOCMs. Results of multivariable modeling revealed no differences in MARCE rates between iohexol and other LOCMs. When direct comparisons of iohexol vs. ioversol and iopamidol were modeled, no differences in MARCE nor the renal component of MARCE were found.

Conclusions: In this retrospective multicenter study, there were no differences in MARCE events with iohexol compared to other LOCMs during inpatient interventional cardiovascular procedures.

Keywords: catheterization, comparative effectiveness/patient centered outcomes research, contrast agents, diagnostic, percutaneous coronary intervention (PCI)

1 | INTRODUCTION

Interventional cardiovascular procedures are often essential for the diagnosis and treatment of coronary artery disease (CAD) and peripheral arterial disease (PAD). According to a recent American Heart Association update, approximately 1 million cardiac catheterizations in addition to half a million percutaneous coronary interventions (PCI) are performed annually in the United States (US). Contrast media play an important role in these procedures and are classified according to their ionic and osmotic properties. Low osmolar contrast media (LOCMs)
include iohexol (Omnipaque), a nonionic, iodinated LOCM. Iohexol as well as other nonionic LOCMs (ioversol [Optiray], ioxilan [Oxilan], iopamidol [Isovue] and ioxaglate [Hexabrix], an ionic LOCM) are commonly used contrast media for computed tomography (CT) imaging and can be administered either intra-arterially or intravenously.

Although LOCMs have a good safety profile, the possibility of adverse reactions such as acute kidney injury (AKI) should always be considered.²⁻³ The development of contrast-induced AKI (CI-AKI) has been widely documented in the literature and the risk factors of CI-AKI are generally known to include the presence of diabetes and the patient’s estimated glomerular filtration rate.⁴ CI-AKI is defined as acute renal insufficiency occurring in a patient with normal renal function preceding CM administration or when a patient with chronic renal insufficiency experiences a significant worsening of renal function after CM administration. In some patients, CI-AKI has been associated with progression to advanced stages of chronic kidney disease and an increased risk for major adverse cardiac events (MACE).⁵⁻⁶ For example, contemporary insights from the NCDR Cath-PCI registry suggest worsened incidence of bleeding, MI, and death attributed to the development of AKI after PCI.⁷

There are a considerable number of reports evaluating the safety of contrast media, though the study methods and findings are variable.⁸⁻¹³ There are several meta-analyses of randomized controlled trials (RCT), comparing CI-AKI rates between LOCMs and iso-osmolar CM (IOCMs).⁸⁻¹¹⁻¹³ Heinrich and coauthors published a meta-analysis in 2009 which indicated that iohexol had higher rates of CI-AKI when compared to IOCMs for coronary angiography. A similar study in 2009 showed that both iohexol and ioxaglate had higher rates of CI-AKI when compared with IOCMs.¹³ Citing these two findings, the 2009 American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines¹⁴ recommend the use of LOCMs other than iohexol and ioxaglate for coronary angiography procedures. However, the guidelines have since changed. The 2011 ACC/AHA guidelines no longer differentiated among LOCMs, and stated “these clinical inferences must be tempered by the relative paucity of head-to-head trials comparing CIN rates among the various contrast media and the variability in results”.¹⁵ Recommendations now encompass three pillars: risk assessment, importance of hydration strategies, and contrast media volume reduction. In a more recent (2012) large retrospective observational study, the safety of various LOCMs was evaluated in patients undergoing inpatient coronary angiography with or without PCI. No apparent clinical advantage was evident amongst LOCMs in regards to in-hospital death, need for hemodialysis, or readmission for CI-AKI.¹⁰

With this background, we set out to describe current outcomes observed in patients receiving various LOCMs from a very large database. The primary objective of this study was to retrospectively assess the rate of major adverse renal or cardiac events (MARCE) when iohexol, compared to other LOCMs, is used during interventional cardiovascular procedures across different hospitals in a real-world setting with, data permitting, direct comparisons of iohexol to iopamidol and ioversol.

2 | METHODS

2.1 | Data source

Data for this study were derived from the Premier Hospital Database, from January 1, 2010 through September 30, 2015. The database contains data from more than 350 million patient encounters, or one in every five discharges in the US.¹⁶ The database includes data from standard hospital discharge files, including a patient’s demographic information, diagnoses, and information on billed services, including medications, laboratory, diagnostics and therapeutic services in deidentified patient daily service records. In addition, information on hospital characteristics, including geographic location, bed size and teaching status is also available. The Premier Hospital Database has been used in over 430 peer reviewed publications. The methods used in this paper provide a general framework for analysis of this database.

Preliminary comparisons between patient and hospital characteristics for the hospitals that submit data to Premier and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS)¹⁷ suggest that the patient populations are similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis, and primary procedure groups. It should be noted that the number of participating hospitals within the database may change over time during the study period.

All data used to perform this analysis were de-identified and accessed in compliance with the Health Insurance Portability and Accountability Act. As a retrospective analysis of a deidentified database, the research was exempt from IRB review under 45 CFR 46.101(b)(4).

2.2 | Inclusion criteria and cohort definitions

Inpatient visits with a primary interventional cardiovascular procedure (Supporting Information Appendix A for coding) were included for analysis. Patient encounters were required to have a record of a single, known LOCM (iohexol, ioversol, ioxilan, ioxaglate, or iopamidol). Visits with an unknown type of contrast (not enough detail in the billing description), IOCM, multiple types of contrast, or no contrast at all were excluded. The attrition diagram (Figure 1) shows the implementation of the inclusion criteria down to the final sample.

2.3 | Outcomes

The primary outcome of interest for this study was the composite end point MARCE. MARCE was defined as having occurred in any inpatient visit if one or more of the following events were recorded: renal failure with dialysis, AKI with and without dialysis, CI-AKI, acute myocardial infarction, angina, stent occlusion/thrombosis, stroke, transient ischemic attack (TIA), or death. To increase the likelihood that the MARCE events were associated with the hospitalization and not conditions present upon admission, events were identified as being an outcome of interest if two conditions were met: (1) record of the event of interest during hospitalization and (2) the event of interest was not coded as present on admission.
2.4 | Univariate comparisons

Patient demographics (age, race, gender, marital status, region, and insurance type), the Elixhauser Comorbidity Index\textsuperscript{18} (Supporting Information Appendix B), hospital characteristics, and MARCE events (Supporting Information Appendix C) were summarized with percentages by each cohort: iohexol vs. other LOCMs. Univariate tests (t tests, chi-squared) were performed to show if significant differences existed between the two cohorts before modeling.

2.5 | Multivariable models

The decision to utilize a particular product or drug during a hospital visit may depend on formal hospital guidelines, patient comorbidities, physician practice patterns or preferences, negotiated reimbursement schedules with insurance companies, and other local (geographic and/or hospital) characteristics. These elements are mostly unobservable for the purpose of statistical inference. In this study, multivariable regression analysis was conducted using the hospital fixed-effects specification to assess the relationship between the type of CM used and MARCE events. The hospital fixed-effect specification methodology was chosen to control for time-invariant within-hospital variation that are otherwise unobservable in the choice of CM, such as hospital protocols which specify which contrast media is used. The fixed-effects model allowed for control of hospitals’ unobserved internal rules on product assignment (hospital indicator). In addition, all models controlled for the following covariates: patient demographics (year, age, gender, race marital status, admission type, and insurance group), comorbidities (categories of the Elixhauser Comorbidity Index) and reason for hospitalization (primary procedure and primary diagnosis).

2.6 | Sensitivity analysis

The other LOCM cohort was further subdivided by each of the individual LOCMs that comprised the group: ioversol, ioxilan, ioxaglate, and iopamidol. Separate models, sample size permitting, were estimated to assess the relationship between MARCE events and iohexol vs. each individual LOCM. Each model used the same hospital fixed-effect specification methodology along with controlling for patient demographics, patient comorbidities and reason for hospitalization.

3 | RESULTS

A total of 1,419,509 inpatient visits from January 2010 through September 2015 met the initial inclusion criterion, having a record of a primary interventional cardiology procedure (Figure 1). Visits were further subdivided into five mutually exclusive categories: (1) no record of contrast usage; (2) visits with multiple contrast usage; (3) visits with contrast usage for which type of contrast was not discernable; (4) visits with a record of IOCM (11%) instead of LOCM; (5) record of single known LOCM. A total of 458,091 (32%) patient encounters met all of the inclusion criteria (primary interventional cardiology procedure with use of a known LOCM). These were divided into two cohorts: iohexol 118,476 (26%) and all other LOCMs 339,615 (74%). The other LOCMs cohort had the following distribution of CM: ioversol (55%), iopamidol (43%), ioxilan (2%), and ioxaglate (0.002%).

3.1 | Univariate

Univariate analysis of the cohorts found no significant difference in the mean age of the cohorts, but statistically significant differences in other demographic characteristics existed (Table 1); however, many of these differences were quite small and potentially due to the very large sample sizes. Iohexol had higher rates of use in Caucasian and male patients. There were also slight differences in insurance provider and admission type. Patient comorbidity scores were slightly higher in the iohexol cohort, whereby iohexol cohort had significantly higher rates of valvular disease (17% vs. 14%, P = 0.0001), cardiac arrhythmia (41% vs. 38%, P = 0.0001), and depression (10% vs. 9%, P = 0.0001) (Table 2). While
the other LOCMs cohort had significantly higher rates of peripheral vascular disorders (18% vs. 16%, \(P \leq 0.0001\)), complicated hypertension (17% vs. 15%, \(P \leq 0.0001\)), and a history of chronic renal failure upon admission to the hospital (16% vs. 14%, \(P \leq 0.0001\)).

The iohexol cohort had a significantly different distribution of hospital region (\(P \leq 0.0001\)), compared with the other LOCMs cohort, with more visits coming from the northeast and west (Table 3). Also, the iohexol cohort had more visits from urban hospitals (\(P \leq 0.0001\)), teaching hospitals (\(P \leq 0.0001\)), and larger bed size hospitals (\(P \leq 0.0001\)). The univariate MARCE rates were slightly higher in the other LOCMs cohort (7.9% vs. 7.7%, \(P = 0.0077\)) before multivariable modeling (Table 4).

### 3.2 | Multivariable

Using the hospital fixed-effects specification, while controlling for patient demographics, comorbid conditions, and primary diagnosis/procedure, differences in MARCE rates between iohexol and other LOCMs were not statistically significant (Figure 2). When analyzing the individual components of the MARCE composite endpoint, iohexol had a slightly higher estimated incidence of stent occlusion/thrombosis (0.0013 [0.0004, 0.0021]) and a lower estimated incidence of angina (−0.0024 [−0.0031, −0.0016]). All other components of MARCE were not statistically significant when comparing iohexol vs. other LOCMs.

### 3.3 | Sensitivity analysis

As a sensitivity analysis, the MARCE and renal composite endpoints were analyzed separately comparing iohexol vs. ioversol and iohexol vs. iopamidol without finding significant differences (Figure 3). There was insufficient sample size to directly compare iohexol with ioxaglate or ioxilan.

### 4 | DISCUSSION

Despite prior concerns regarding iohexol, we found no evidence of increased MARCE among those who received iohexol as compared to
other LOCMs. While many prior studies have evaluated the safety profile of LOCMs using serum creatinine, this is the first to use real-world data to compare clinical outcomes when using iohexol vs. other LOCMs during interventional cardiovascular procedures.

In our study, there was no difference among LOCMs for most individual components of the composite MARCE endpoint, including stroke, TIA, AKI, renal failure, and death. However, results of the univariate analysis indicated patients who received iohexol had lower AKI and CI-AKI. Results of the multivariable analysis indicated there was no statistically significant difference in the risk of MARCE when iohexol was used compared to other LOCMs. A sensitivity analysis also was conducted comparing iohexol to each of the other LOCMs individually, which showed a non-significant difference in MARCE rates between iohexol and ioversol or iopamidol. There was insufficient data available for a direct head-to-head comparison between iohexol and ioxaglate or ioxilan.

Adverse event rates associated with LOCMs have been studied extensively and while this study shows no difference in the rate of the MARCE composite, results of prior published studies have varied. Meta-analyses of available RCTs have been published comparing LOCMs and IOCMs, the overlap in time-periods and inclusion criteria led to the use of some of the same trials in multiple studies. In a meta-analysis of CI-AKI rates between LOCMs and an IOCM, no difference was reported between CI-AKI rates with all LOCMs grouped together, a subgroup analysis separately comparing iohexol with IOCM and all other LOCMs (grouped together) with IOCMs found iohexol had significantly higher CI-AKI rates. The group containing all other LOCMs was still not statistically different. A very similar

| Elixhauser comorbidities | Iohexol | Percent | Other LOCMs | Percent | P-value |
|--------------------------|---------|---------|-------------|---------|---------|
| Total visits             | 118,476 | 100%    | 339,615     | 100%    |         |
| Elixhauser comorbidities |         |         |             |         |         |
| Congestive heart failure | 31,120  | 26%     | 87,272      | 26%     | 0.0001  |
| Cardiac arrhythmia       | 49,093  | 41%     | 129,093     | 38%     | <.0001  |
| Valvular disease         | 20,119  | 17%     | 48,875      | 14%     | <.0001  |
| Pulmonary circulation disorders | 6,777 | 6%       | 19,401      | 6%      | 0.9237  |
| Peripheral vascular disorders | 19,335 | 16%      | 62,682      | 18%     | <.0001  |
| Hypertension (uncomplicated) | 73,312 | 62%      | 209,089     | 62%     | 0.0566  |
| Hypertension (complicated) | 17,781 | 15%      | 56,072      | 17%     | <.0001  |
| Paralysis                | 1,513   | 1%      | 3,797       | 1%      | <.0001  |
| Other neurological disorders | 6,985  | 6%      | 18,264      | 5%      | <.0001  |
| Chronic pulmonary disease | 27,871 | 24%     | 81,730      | 24%     | 0.0002  |
| Diabetes (uncomplicated) | 36,330  | 31%     | 106,824     | 31%     | <.0001  |
| Diabetes (complicated)   | 6,654   | 6%      | 20,155      | 6%      | <.0001  |
| Hypothyroidism           | 12,993  | 11%     | 36,127      | 11%     | 0.0015  |
| Renal failure            | 16,875  | 14%     | 53,447      | 16%     | <.0001  |
| Liver disease            | 3,045   | 3%      | 8,485       | 2%      | 0.1748  |
| Peptic ulcer disease (excluding bleeding) | 740 | 1% | 2,256 | 1% | 0.1446 |
| AIDS/HIV                 | 189     | 0%      | 511         | 0%      | 0.4917  |
| Lymphoma                 | 540     | 0%      | 1,597       | 0%      | 0.5297  |
| Metastatic cancer        | 474     | 0%      | 1,453       | 0%      | 0.2037  |
| Solid tumor without metastasis | 1,606 | 1%      | 4,769       | 1%      | 0.2180  |
| Rheumatoid arthritis collagen | 2,457 | 2% | 6,427 | 2% | <.0001 |
| Coagulopathy             | 7,562   | 6%      | 20,232      | 6%      | 0.0020  |
| Obesity                  | 21,080  | 18%     | 60,936      | 18%     | 0.2461  |
| Weight loss              | 2,980   | 3%      | 7,770       | 2%      | <.0001  |
| Fluid and electrolyte disorders | 21,400 | 18% | 60,178 | 18% | 0.0078 |
| Blood loss anemia        | 717     | 1%      | 2,404       | 1%      | 0.0002  |
| Deficiency anemia        | 2,167   | 2%      | 6,738       | 2%      | 0.0009  |
| Alcohol abuse            | 3,969   | 3%      | 10,423      | 3%      | <.0001  |
| Drug abuse               | 3,035   | 3%      | 8,127       | 2%      | 0.0012  |
| Psychoses                | 963     | 1%      | 2,736       | 1%      | 0.8114  |
| Depression               | 11,596  | 10%     | 29,058      | 9%      | <.0001  |
| Elixhauser comorbidity index |       |         |             |         | <.0001  |
| Mean                     | 3.5     |         | 3.4         |         |         |
| Std. dev.                | 2.22    |         | 2.19        |         |         |
meta-analysis showed that both iohexol and ioxaglate had higher CI-AKI rates than an IOCM. It is important to note that there is no published RCT directly comparing individual LOCMs in a head-to-head fashion. Prior published results performed indirect comparisons, whereas the current study directly compared various LOCMs head-to-head in a real-world setting. Moreover, the published meta-analyses only evaluate CI-AKI as a biochemical endpoint, whereas this study evaluated a clinical composite endpoint capturing many different adverse events not evaluated in prior studies.

Results of this analysis confirm and extend the results of a large retrospective, propensity-matched observational study which revealed no difference in hemodialysis, readmission due to CI-AKI, or mortality between iohexol, ioversol or iopamidol. Our study adds to the literature with the composite endpoint of MARCE and with detailed statistical management of patient demographics, patient comorbidities, reason for hospitalization and within hospital variation to arrive at independent measures of risk for each CM. The MARCE events we reported occurred in the same visit as contrast exposure and thus it is likely that the procedure and use of contrast were clinically associated in some way with the MARCE event(s) that occurred.

4.1 | Strengths and limitations
The strengths of this study include the use of a comprehensive data source and use of the hospital fixed-effect specification methodology that controlled for time-invariant within hospital variation that

| TABLE 3 | Hospital baseline characteristics |
|---|---|---|---|
| | Iohexol | Other LOCMs | |
| Total visits | N | Percent | N | Percent | P-value |
| Census region | | | | | <.0001 |
| Northeast | 23,928 | 20% | 48,535 | 14% | |
| Midwest | 21,323 | 18% | 60,034 | 18% | |
| South | 54,570 | 46% | 194,610 | 57% | |
| West | 18,655 | 16% | 36,436 | 11% | |
| Location | | | | | <.0001 |
| Urban | 111,774 | 94% | 306,937 | 90% | |
| Not urban | 6,702 | 6% | 32,678 | 10% | |
| Type | | | | | <.0001 |
| Teaching | 71,661 | 60% | 162,953 | 48% | |
| Non-teaching | 46,815 | 40% | 176,662 | 52% | |
| Bed count | | | | | <.0001 |
| 0–99 | 865 | 1% | 5,715 | 2% | |
| 100–199 | 9,741 | 8% | 23,291 | 7% | |
| 200–299 | 9,998 | 8% | 42,733 | 13% | |
| 300–399 | 16,922 | 14% | 79,258 | 23% | |
| 400–499 | 21,512 | 18% | 56,274 | 17% | |
| 500+ | 59,438 | 50% | 132,344 | 39% | |

| TABLE 4 | Rates of adverse events prior to multivariable modeling |
|---|---|---|---|
| | Iohexol | Other LOCMs | |
| Total visits | N | Percent | N | Percent | P-value |
| Adverse events | | | | | | |
| MARCE | 9,076 | 7.7% | 26,837 | 7.9% | 0.0077 |
| AMI | 1,131 | 1.0% | 2,822 | 0.8% | <.0001 |
| Angina | 375 | 0.3% | 1,212 | 0.4% | 0.0418 |
| Stent | 490 | 0.4% | 1,601 | 0.5% | 0.011 |
| Stroke | 1,133 | 1.0% | 3,153 | 0.9% | 0.3903 |
| TIA | 163 | 0.1% | 531 | 0.2% | 0.1526 |
| Renal composite | 4,643 | 3.9% | 14,051 | 4.1% | 0.0011 |
| Acute kidney injury | 4,627 | 3.9% | 13,999 | 4.1% | 0.0012 |
| Acute kidney injury with dialysis | 297 | 0.3% | 895 | 0.3% | 0.4547 |
| Acute kidney injury, contrast induced | 244 | 0.2% | 976 | 0.3% | <.0001 |
| Renal failure | 17 | 0.0% | 54 | 0.0% | 0.7119 |
| Death | 2,349 | 2.0% | 6,965 | 2.1% | 0.1523 |

Abbreviations: AMI, acute myocardial infarction; TIA, transient ischemic attack.
is otherwise unobservable, such as physician preferences and internal protocols. This study has limitations, which are inherent to retrospective database analyses. These include the unit of inference, which was the visit and not the patient, and the lack of longitudinal tracking of a patient. Thus, it was not possible to determine if events occurred after the patient was discharged. Laboratory values were not available, thus we could not define CI-AKI by serum creatinine levels, and rather the outcome was defined by the ICD-9 code for CI-AKI which may underestimate the occurrence of this event. The data source for this study was the Premier Healthcare Database which represents 20% of all inpatient discharges in the US; however, given its reliance on ICD-9 codes, even with validation efforts, the risk of coding errors cannot be completely eliminated. Additionally, CM volume is not a data point that is captured in this hospital billing database. Attempts to identify the CM volume used, through text mining the chargemaster of this database, were not successful at a high enough frequency, resulting in a large portion of missing data for patients. Even if this portion of data was not missing, there is a potential of an overestimation based on use of the total amount that is charged for the visit, and not what was actually administered. This overestimation could be biased toward each type of CM differently, given the variation in package sizing.

5 | CONCLUSION

This analysis used multivariable modeling to control for differences in hospital characteristics, patient demographics and comorbidities across the LOCM cohorts. This retrospective study found no statistically significant clinical differences in the rate of MARCE among those given iohexol compared to patients who received other LOCMs combined and specifically vs. ioversol and iopamidol for inpatient interventional cardiovascular procedures.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: McCullough PA, Todoran TM, Brilakis ES, Ryan MP, Gunnarsson C. Rate of major adverse renal or cardiac events with ioxiflo compared to other low osmolar contrast media during interventionl cardiovascular procedures. Catheter Cardiovasc Interv. 2019;93:E90-E97. https://doi.org/10.1002/ccd.27807