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ORIGINAL STUDIES

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

Peter A. McCullough MD, MPH[1,2,3,4] | Thomas M. Todoran MD[5,6] |
Emmanouil S. Brilakis MD, PhD[7,8] | Michael P. Ryan MS[9] | Candace Gunnarsson EdD[9]

[1]Baylor University Medical Center, Dallas, Texas

[2]Baylor Heart and Vascular Institute, Dallas, Texas

[3]Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, Texas

[4]Texas A&M Health Science Center College of Medicine, Dallas, Texas

[5]Medical University of South Carolina, Charleston, South Carolina

[6]Ralph H. Johnson VA Medical Center, Charleston, South Carolina

[7]Minneapolis Heart Institute, Minneapolis, Minnesota

[8]University of Texas, Southwestern Medical Center, Dallas, Texas

[9]Real World Evidence, CTI Clinical Trial & Consulting Services, Covington, Kentucky

Correspondence
Candace Gunnarsson EdD, CTI Clinical Trial and Consulting Services, Inc., 100 E. RiverCenter Boulevard, Covington, KY 41011.
Email: cgunnarsson@ctifacts.com

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).[1] 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 Guidelines[14] 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.
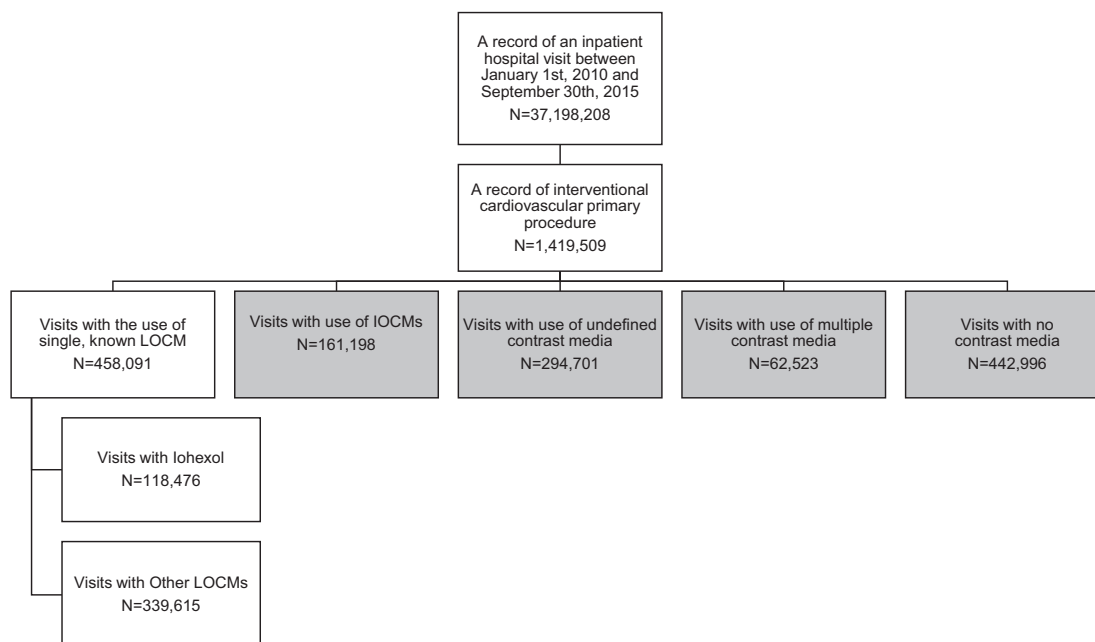
FIGURE 1 Attrition diagram. LOCM: low osmolar contrast media including ioversol, ioxilan, ioxaglate, or iopamidol

2.4 | Univariate comparisons

Patient demographics (age, race, gender, marital status, region, and insurance type), the Elixhauser Comorbidity Index[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%, $P \leq 0.0001$), cardiac arrhythmia (41% vs. 38%, $P \leq 0.0001$), and depression (10% vs. 9%, $P \leq 0.0001$) (Table 2). While

TABLE 1 Patient visit baseline demographics

	Iohexol		Other LOCMs		
	N	Percent	N	Percent	P-value
Total visits	118,476	100%	339,615	100%	
Age					0.3525
Median	65		65		
Mean	64.9		64.9		
Std. dev.	13.08		13.07		
Age group					0.0694
<18	280	0%	913	0%	
18–29	614	1%	1,632	0%	
30–39	2,406	2%	6,904	2%	
40–49	10,690	9%	30,269	9%	
50–59	25,668	22%	72,867	21%	
60–69	33,752	28%	97,687	29%	
70–79	28,130	24%	81,174	24%	
80 or older	16,936	14%	48,169	14%	
Race					<.0001
Caucasian	90,443	76%	249,213	73%	
African-American	11,587	10%	35,601	10%	
Other	16,446	14%	54,801	16%	
Gender					<.0001
Female	41,234	35%	120,999	36%	
Male	77,241	65%	218,614	64%	
Unknown	1	0%	2	0%	
Insurance					<.0001
Commercial	6,421	5%	15,607	5%	
Medicare	67,091	57%	190,232	56%	
Medicaid	8,296	7%	24,976	7%	
Managed care	25,460	21%	77,482	23%	
Other	11,208	9%	31,318	9%	
Admission type					<.0001
Emergency	60,628	51%	182,853	54%	
Urgent	26,754	23%	64,574	19%	
Elective	30,817	26%	88,330	26%	
Other/unknown	277	0%	3,858	1%	

the other LOCMs cohort had significantly higher rates of peripheral vascular disorders (18% vs. 16%, P ≤ 0.0001), complicated hypertension (17% vs. 15%, P ≤ 0.0001), and a history of chronic renal failure upon admission to the hospital (16% vs. 14%, P ≤ 0.0001).

The iohexol cohort had a significantly different distribution of hospital region (P ≤ 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 ≤ 0.0001), teaching hospitals (P ≤ 0.0001), and larger bed size hospitals (P ≤ 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

TABLE 2 Patient baseline comorbid conditions

	Iohexol		Other LOCMs		
	N	Percent	N	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%	18,646	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	12,995	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%	20,823	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		

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[8-13] 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,[8,11-13] 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.[12] The group containing all other LOCMs was still not statistically different. A very similar

TABLE 3 Hospital baseline characteristics

	Iohexol		Other LOCMs		
	N	Percent	N	Percent	P-value
Total visits	118,476	100%	339,615	100%	
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%	

meta-analysis showed that both iohexol and ioxaglate had higher CI-AKI rates than an IOCM.[13] 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[10] 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 4 Rates of adverse events prior to multivariable modeling

	Iohexol		Other LOCMs		
	N	Percent	N	Percent	P-value
Total visits	118,476	100%	339,615	100%	
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

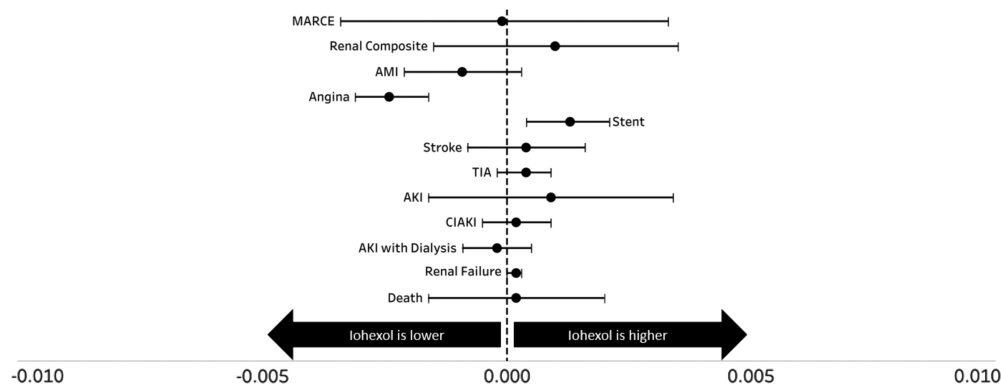Abbreviations: AMI, acute myocardial infarction; TIA, transient ischemic attack.

FIGURE 2 Multivariable model results—iohexol vs. other LOCMs. The parameter estimates with confidence intervals from multivariable modeling which used the hospital fixed-effects specification, and controlled for patient demographics, comorbid conditions, and primary diagnosis/procedure, are shown. The composite endpoint of the rate of MARCE was found to have no statistically significant differences between iohexol and other LOCMs. Rates of the individual components of the MARCE composite endpoint were analyzed, iohexol had a slightly higher estimate of stent occlusion/thrombosis (0.0013 [0.0004, 0.0021]) and a lower estimate of angina (−0.0024 [−0.0031, −0.0016]). All other components of MARCE were not statistically significant when comparing iohexol vs. other LOCMs. MARCE: major adverse renal or cardiac events, LOCM: low osmolar contrast media, AMI: acute myocardial infarction, TIA: transient ischemic attack, AKI: acute kidney injury, CI-AKI: contrast induced acute kidney injury
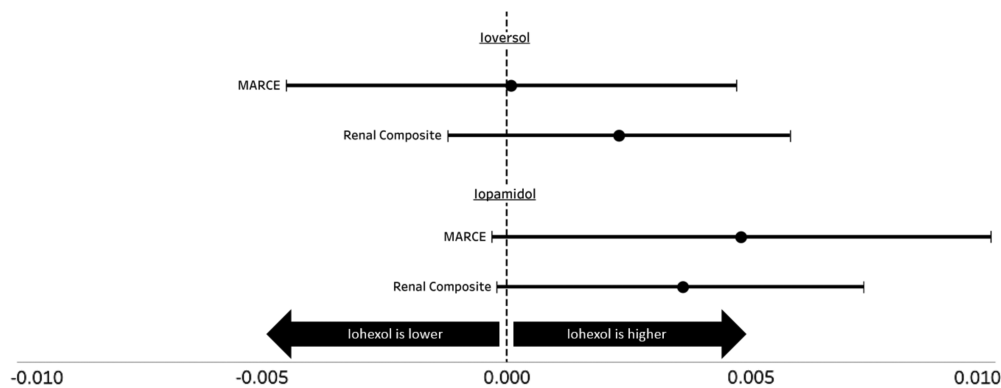

FIGURE 3 Multivariable model results—iohexol vs. ioversol and iopamidol. The figure shows the parameter estimates with confidence intervals from of a sensitivity analysis in which the MARCE and renal composite endpoints were analyzed separately comparing iohexol to ioversol and iohexol to iopamidol. The sensitivity analysis used multivariable modeling with hospital fixed-effects specification, controlled for patient demographics, comorbid conditions, and primary diagnosis/procedure. No differences were found in the rate of MARCE or renal adverse events between iohexol and ioversol nor between iohexol and iopamidol. MARCE: major adverse renal or cardiac events

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.

ORCID

Peter A. McCullough https://orcid.org/0000-0002-0997-6355
Emmanouil S. Brilakis https://orcid.org/0000-0001-9416-9701
Candace Gunnarsson https://orcid.org/0000-0003-0723-585X

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SUPPORTING INFORMATION

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