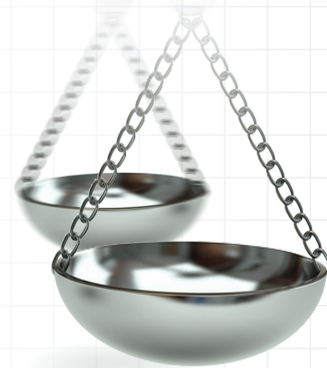




Iso-osmolar contrast media and adverse renal and cardiac events after percutaneous cardiovascular intervention

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Aim: To assess the relationship between type of contrast media (CM), iso-osmolar contrast media (IOCM) or low-osmolar contrast media (LOCM), and major adverse renal and cardiovascular events (MARCE). **Materials & methods:** Coronary or peripheral angioplasty visits were stratified into CM cohorts: IOCM or LOCM. Multivariable regression analysis used hospital fixed effects to assess the relationship between MARCE events and type of CM. **Results:** Among 333,533 visits (357 hospitals), the incidence of MARCE was 7.41%. After controlling for observable and unobservable time invariant within-hospital characteristics, administration of IOCM versus LOCM was associated with a 0.69% absolute and 9.32% relative risk reduction in MARCE rate. **Conclusion:** Our study indicates that as compared with LOCM, IOCM may be associated with reduction of MARCE events in coronary or peripheral angioplasty patients.

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Keywords: angioplasty • low-osmolar contrast media • major adverse renal and cardiovascular events (MARCE) • relative risk

Arterial angiography and percutaneous intervention require administration of iodinated contrast media (CM) to render the blood vessels radiographically opaque. Contrast-induced acute kidney injury (CI-AKI) is one of the major adverse events associated with administration of iodinated CM [1,2]. The most common definition of CI-AKI is a rise in serum creatinine levels by ≥ 0.3 mg/dl within 48 h of contrast administration. CI-AKI has been associated with progression to advanced stages of chronic kidney disease (CKD) and with increased risk for major adverse cardiac events (MACE) [3,4].

CI-AKI is the third most common cause of hospital-acquired renal failure and is associated with increased morbidity, prolonged hospitalization and higher rates of in-hospital and long-term mortality [5,6]. The incidence of CI-AKI varies from 2% in the general population to over 50% in high-risk groups [7]. In studies of the impact of the osmolality of iodinated CM, the use of low-osmolar contrast media (LOCM) has been shown to substantially reduce the risk of nephropathy when compared with high-osmolar CM [8–11].

In several studies, iodixanol, iso-osmolar contrast media (IOCM) have been associated with lower risk for CI-AKI when compared with LOCM [12–16]. In a meta-analysis of 16 randomized controlled trials, McCullough *et al.* found that CI-AKI occurred less frequently for all patients in the iodixanol group when compared with the LOCM group [15]. Similar findings were reported for the subgroup of patients with CKD and for patients with CKD and diabetes mellitus. More recent meta-analysis concluded that iodixanol use was associated with less nephrotoxicity compared with LOCM and that use of iodixanol was associated with significantly fewer contrast-induced nephropathy events compared with LOCM [12]. Both meta-analyses concluded that intra-arterial

administration of iodixanol may be the more appropriate choice of CM among high-risk CKD and CKD diabetes mellitus patients [12,16].

Patients who survive an episode of AKI are at risk for progression to advanced stages of CKD [17–20]. As a result, the composite end point of major adverse kidney events (MAKE) was endorsed by the National Institute of Diabetes and Digestive and Kidney Diseases clinical trials workgroup to harmonize and encourage future clinical trials [21]. AKI is associated with the development of CKD, which is known to be a risk factor for MACE including nonfatal myocardial infarction, stroke and cardiovascular death [22,23]. A retrospective study of the veteran population assessed the development of the combination of MAKE and MACE – major adverse renal and cardiovascular events (MARCE) – and demonstrated their relationships to mortality [18]. Whether use of IOCM is associated with lower risk for MARCE has not been completely elucidated due to small sample sizes and limited follow-up.

Currently, the evidence to support the use of CM is derived from randomized clinical trials and meta-analyses of clinical trial data; however, there is little evidence examining the benefits of IOCM versus a LOCM agent in the real-world setting where the choice of agents is influenced by availability, internal hospital protocols, purchasing agreements, physician/technician preference, presence of allergic reactions, hemodynamic instability and risk for CI-AKI. Therefore, the objective of this study was to retrospectively assess the relationship between the type of CM (IOCM or LOCM) and MARCE events in patients undergoing inpatient arterial (coronary, carotid and peripheral) angiography and intervention across different hospitals in a real-world setting.

Materials & methods

Data source

The premier database was used as the data source for this study. This database contains data from more than 580 million patient encounters or one in every five discharges in the USA [24]. The premier database contains data from standard hospital discharge files, including a patient's demographic and disease state and information on billed services, including medications, laboratory, diagnostics and therapeutic services in de-identified patient daily service records. In addition, information on hospital characteristics, including geographic location, bed size and teaching status, is also available. 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 suggest that the patient populations are similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups.

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 de-identified database, the research was exempt from IRB review under 45 CFR 46.101(b)(4).

Inclusion & exclusion criteria

Any inpatient hospital visits in the premier database from 1 January 2008 through 30 September 2013 were eligible for inclusion. Inpatient was defined as a visit which included an overnight stay. Visits were required to include one of the following primary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure code for angioplasty: 00.61 Percutaneous angioplasty or atherectomy of precerebral (extracranial) vessel(s), 00.62 Percutaneous angioplasty or atherectomy of intracranial vessel(s), 00.66 Percutaneous transluminal coronary angioplasty or coronary atherectomy or 39.50 Angioplasty or atherectomy of other noncoronary vessel(s). Visits were excluded if [1] CM utilization was unidentified or [2] the same visit had a record of utilizing both IOCM and LOCM.

Cohort definitions

Patients cannot be tracked over time in the Premier Hospital database. Therefore, the data captured for this analysis were a patient's hospitalization when the primary reason for the visit was an inpatient angioplasty. All inpatient vascular intervention (see definition above) visits meeting the inclusion criteria were stratified into two cohorts based on the CM agents identified by Standard Charge Master Codes and text mining algorithms. The two cohorts were [1] IOCM (iodixanol) and [2] LOCM (iohexol, ioversol, iopamidol, ioxaglate, ioxilan and iopromide).

Primary outcome

The primary outcome of interest was the renal and cardiovascular major adverse event 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 or without dialysis, CI-AKI, acute myocardial infarction (AMI), angina, stent occlusion/thrombosis, stroke, transient ischemic attack or death. Supplementary Table 1 gives a complete listing of these events with the corresponding diagnosis codes used for identification. Safeguards were put in place to make sure that events of interest (MARCE, AMI, etc.) were associated with the hospitalization and not conditions the patient had upon admission. For this analysis, 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 present on admission. Subanalyses were performed separately for the following outcomes of interest [1]: renal composite consisting of renal events that required dialysis [2], AMI [3], angina and [4] stent occlusion/thrombosis.

Model inputs

Patient demographics (age, race, gender, marital status, region and insurance type) and specific comorbid conditions (hypertension, hypotension, diabetes, renal disease and dehydration) as well as the Charlson Comorbidity Index [25] and risk of severity and mortality associated with the angioplasty visit were summarized with percentages by each cohort: IOCM versus LOCM (Table 1) (see Supplementary Table 2 for comorbidities and associated ICD-9 codes included in the Charlson Comorbidity Index). The risk of severity and mortality is calculated based on the 3M All Patient Refined Diagnosis Related Groups Classification System (3M Health Information Services) [26]. This index is a widely adopted proprietary risk adjustment classification tool, which uses information from routine claims data to produce valid and reliable severity measurement and risk adjustment scores. It is used to account for differences related to an individual's severity of illness or risk of mortality in large datasets. Severity of illness refers to the extent of physiologic decompensation or organ system loss of function. Risk of mortality refers to the likelihood of dying. Each of these scores use a category from 1 to 4 which indicate minor, moderate, major or extreme severity of illness or risk of mortality. The patients' All Patient Refined Diagnosis Related Groups score is based on the underlying diagnoses; patients with high severity of illness or risk of mortality generally have multiple comorbid conditions or multiple serious diseases, which represent difficulty to treat patients [27].

Recent published evidence indicates that contrast volume usage varies by procedure and across operators in routine clinical practice. It should therefore be considered as a model input. For example, Amin *et al.* found that in patients having percutaneous cardiovascular intervention the average amount of contrast physicians delivered varied from 79 to 487 ml [28]. In this study, the total volume (milliliter) of CM used during the visit was calculated by text mining of each visit's billing file. The availability of this data was limited due to missing fields in the billing file and a proxy (potential overestimate); since it was determined by how much CM was charged on the visit, including unused volumes, and not the actual dose.

Statistical 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. As a result, multivariable regression analysis was conducted using the hospital fixed-effects specification to assess the relationship between MARCE events and type of contrast agent used. Additional end points included renal composite with dialysis, AMI, angina and stent occlusion/thrombosis. The hospital fixed-effect specification methodology was chosen because it controls for time invariant within hospital variation that are otherwise unobservable in the choice of CM, such as hospital protocols that specify when to use IOCM or LOCM. The fixed-effect model specified for the primary end point of MARCE and the subanalyses first included only a hospital fixed-effect control. Each additional model added controls for year fixed effect, procedure fixed effects, patient demographics and comorbid conditions, respectively. Although CM volume estimates were limited due to missing data, this variable was also considered for model inclusion. Using this methodology, the coefficient estimate on the use of IOCM is informed solely by hospitals using both IOCM and LOCM. The fixed-effects model allowed for control of hospitals' unobserved internal rules on product assignment (hospital indicator).

Although all inpatient visits in our sample had a primary procedure code for angioplasty, primary diagnoses varied with coronary atherosclerosis occurring most frequently. Since the risk of MARCE is different for patients undergoing coronary intervention versus carotid or peripheral vascular intervention, a sensitivity analysis was performed by removing patients with a primary diagnosis of peripheral arterial disease (5.2% of the sample) and rerunning the models.

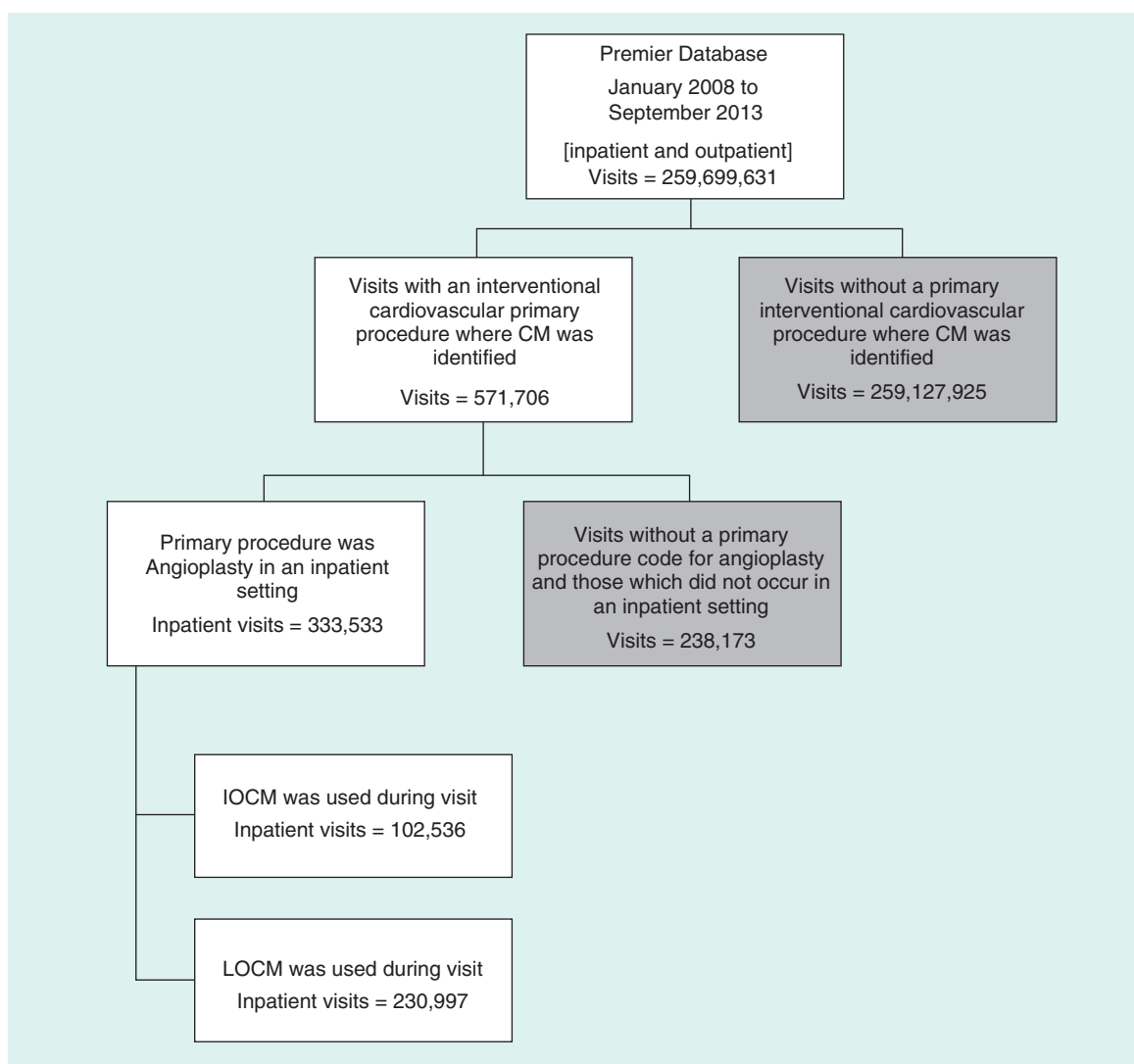


Figure 1. Attrition diagram.

IOCM: Iso-osmolar contrast media; LOCM: Low-osmolar contrast media.

Results

A total of 333,533 primary inpatient angioplasty procedures in 357 hospitals met the study criteria for inclusion in this analysis (Figure 1). IOCM and LOCM were used in 102,536 (30.7%) and 230,997 (69.3%) procedures, respectively. The majority of hospitals (264, 74%) used both CM agents and all model results were based on the hospitals in which both CM agents are used. There was a fairly even split between teaching versus nonteaching hospitals, most of which were facilities with ≥ 400 beds.

Patients who received IOCM were older (66.75 vs 63.82 years; $p < 0.0001$; Table 1) with higher proportion of women (38.23 vs 35.28%; $p < 0.0001$) and primary insurance being Medicare (61.42 vs 52.50%; $p < 0.0001$), as compared with patients receiving LOCM. They were also more likely to be in the 'extreme' category for both severity of illness (7.31 vs 5.00%; $p < 0.0001$) and mortality risk (6.35 vs 4.27%; $p < 0.0001$). IOCM was more commonly used in peripheral procedures.

Patients who were selected for and received IOCM had a greater burden of concomitant illness as reflected by the mean Charlson Comorbidity Index Score (3.9 vs 3.4; $p < 0.0001$; Table 2) and slightly higher length of stay (IOCM mean 3.76 days versus LOCM mean 3.15 days). In particular, IOCM patients had higher rates of diabetes with complications (8.45 vs 4.31%; $p < 0.0001$), hypotension (5.33 vs 4.32%; $p < 0.0001$) and renal disease (23.86 vs 12.60%; $p < 0.0001$). The median CM volume per visit was 200 ml for each cohort.

Table 1. Patient demographics.

Category	IOCM (n = 102,536)	LOCM (n = 230,997)	p-value
Age, mean (SD), (years)	66.75 (12.74)	63.82 (12.5)	<0.0001
Race	Number of patients (%)	Number of patients (%)	<0.0001
– Caucasian	74,609 (72.76)	168,434 (72.92)	
– African–American	11,833 (11.54)	24,428 (10.58)	
– Other	16,094 (15.69)	38,135 (16.51)	
Gender			<0.0001
– Female	39,201 (38.23)	81,503 (35.28)	
– Male	63,334 (61.77)	149,494 (64.72)	
– Unknown	1 (0)	0 (0)	
Marital status			<0.0001
– Married	51,655 (50.38)	123,524 (53.47)	
– Unmarried	40,673 (39.67)	85,228 (36.89)	
– Other/unknown	10,208 (9.96)	22,245 (9.63)	
Insurance			<0.0001
– Commercial	5620 (5.48)	14,504 (6.28)	
– Medicare	62,973 (61.42)	121,274 (52.50)	
– Medicaid	5779 (5.64)	14,571 (6.31)	
– Managed care	20,869 (20.35)	57,040 (24.69)	
– Other	7295 (7.11)	23,608 (10.22)	
Severity of illness[†]			<0.0001
– Minor	29,491 (28.76)	82,988 (35.93)	
– Moderate	40,066 (39.08)	93,907 (40.65)	
– Major	25,483 (24.85)	42,562 (18.43)	
– Extreme	7496 (7.31)	11,540 (5.00)	
Mortality risk[†]			<0.0001
– Minor	42,790 (41.73)	122,925 (53.21)	
– Moderate	36,988 (36.07)	71,860 (31.11)	
– Major	16,244 (15.84)	26,340 (11.40)	
– Extreme	6514 (6.35)	9872 (4.27)	
Type of procedure			<0.0001
– Coronary	73,754 (71.93)	207,008 (89.62)	
– Peripheral	24,518 (23.91)	19,965 (8.64)	
– Carotid	4264 (4.16)	4024 (1.74)	

[†]Severity of illness and mortality risk were calculated using 3 M APR DRG Classification System (3 M Health Information Services).

APR DRG: All Patient Refined Diagnosis Related Group; IOCM: Iso-osmolar contrast media; LOCM: Low-osmolar contrast media; SD: Standard deviation.

Table 3 reports the results of four multivariable regression models using the hospital fixed-effects methodology. Each model in the table has a column label of 1–4 and represents an increase in the degree of model saturation by choice of variables included in the model. For example, model 1 displays the coefficient estimates for the use of IOCM on the primary end point MARCE, as well as each secondary end point (renal composite, AMI, angina and stent occlusion/thrombosis) while only controlling for hospital fixed effects. On the other hand, model 4 displays the coefficient estimates for the use of IOCM on each end point when the model is fully adjusted or saturated; in other words, controlling for hospital fixed effects, year of visit, type of procedure, patient demographics and comorbidities. By displaying the progression of model saturation, one can see the effects of each model adjustment on the use of IOCM for each end point of interest. The transparency of model adjustments are important because it allows the reader to see the effect that different covariates have on the model results. For example, comorbid conditions may be associated with both adverse events and the use of CM, by displaying the progression of model saturation, one can see the effect of including comorbid conditions in the model by comparing the third and fourth columns.

Table 2. Comorbid conditions.

Category	IOCM (n = 102,536)	LOCM (n = 230,997)	p-value
	Number of patients (%)	Number of patients (%)	
Comorbidities			
– Hypertension	80,517 (78.53)	178,386 (77.22)	<0.0001
– Hypotension	5468 (5.33)	9982 (4.32)	<0.0001
– Diabetes without complications	34,324 (33.48)	75,599 (32.73)	<0.0001
– Diabetes with complications	8666 (8.45)	9945 (4.31)	<0.0001
– Renal disease	24,464 (23.86)	29,114 (12.60)	<0.0001
– Renal transplant	745 (0.73)	732 (0.32)	<0.0001
– Dehydration	1332 (1.29)	1954 (0.85)	<0.0001
Charlson score			
– Mean	3.9	3.4	<0.0001
– SD	1.73	1.56	
– Q1	3	2	
– Median	4	3	
– Q3	5	4	
The International Classification of Diseases, Ninth Revision (ICD-9) codes used in the Charlson Comorbidity Index are listed in Supplementary Table 2, ICD-9 codes for listed comorbid conditions are given in Supplementary Table 3.			
IOCM: Iso-osmolar contrast media; LOCM: Low-osmolar contrast media; SD: Standard deviation.			

Table 3. Results of multivariable fixed-effects models: absolute risk reduction when iso-osmolar contrast media is compared with low-osmolar contrast media.

Adverse events – IOCM vs LOCM (n = 333,533)				
MARCE	Model 1	Model 2	Model 3	Model 4
– Estimate	0.0248 [‡]	0.0209 [‡]	0.0131 [‡]	-0.00691 [‡]
– Standard error	[0.00123]	[0.00123]	[0.00124]	[0.00116]
Renal composite				
– Estimate	0.00290 [‡]	0.00225 [‡]	0.00185 [‡]	-0.00208 [‡]
– Standard error	[0.000309]	[0.000310]	[0.000312]	[0.000314]
AMI				
– Estimate	0.000708	0.000479	-0.00063	-0.00355 [‡]
– Standard error	[0.000490]	[0.000493]	[0.000497]	[0.000492]
Angina				
– Estimate	-0.00416 [‡]	-0.00882 [‡]	-0.00856 [‡]	-0.00805 [‡]
– Standard error	[0.000665]	[0.000657]	[0.000663]	[0.000673]
Stent occlusion/thrombosis				
– Estimate	-0.0004	-0.000848 [†]	-0.000817 [†]	-0.00107 [‡]
– Standard error	[0.000337]	[0.000339]	[0.000342]	[0.000347]
Hospital fixed effects	✓	✓	✓	✓
Year fixed effects		✓	✓	✓
Procedure fixed effects		✓	✓	✓
Patient demographics			✓	✓
Patient comorbidities				✓

Model 1 includes absolute risk reduction estimates from the model with no additional adjustments beyond individual hospital indicators; in model 2, the year and procedure indicators were added to the model; in model 3, the patient demographics were added; and model 4 includes patient comorbidities and shows absolute risk reduction estimates of the fully saturated model. Renal composite includes renal events that required dialysis, ICD-9 code 585.6 or 584.9 + 39.95.

[†]p < 0.05;

[‡]p < 0.01.

AMI: Acute myocardial infarction; IOCM: Iso-osmolar contrast media; LOCM: Low-osmolar contrast media; MARCE: Major adverse renal and cardiovascular event.

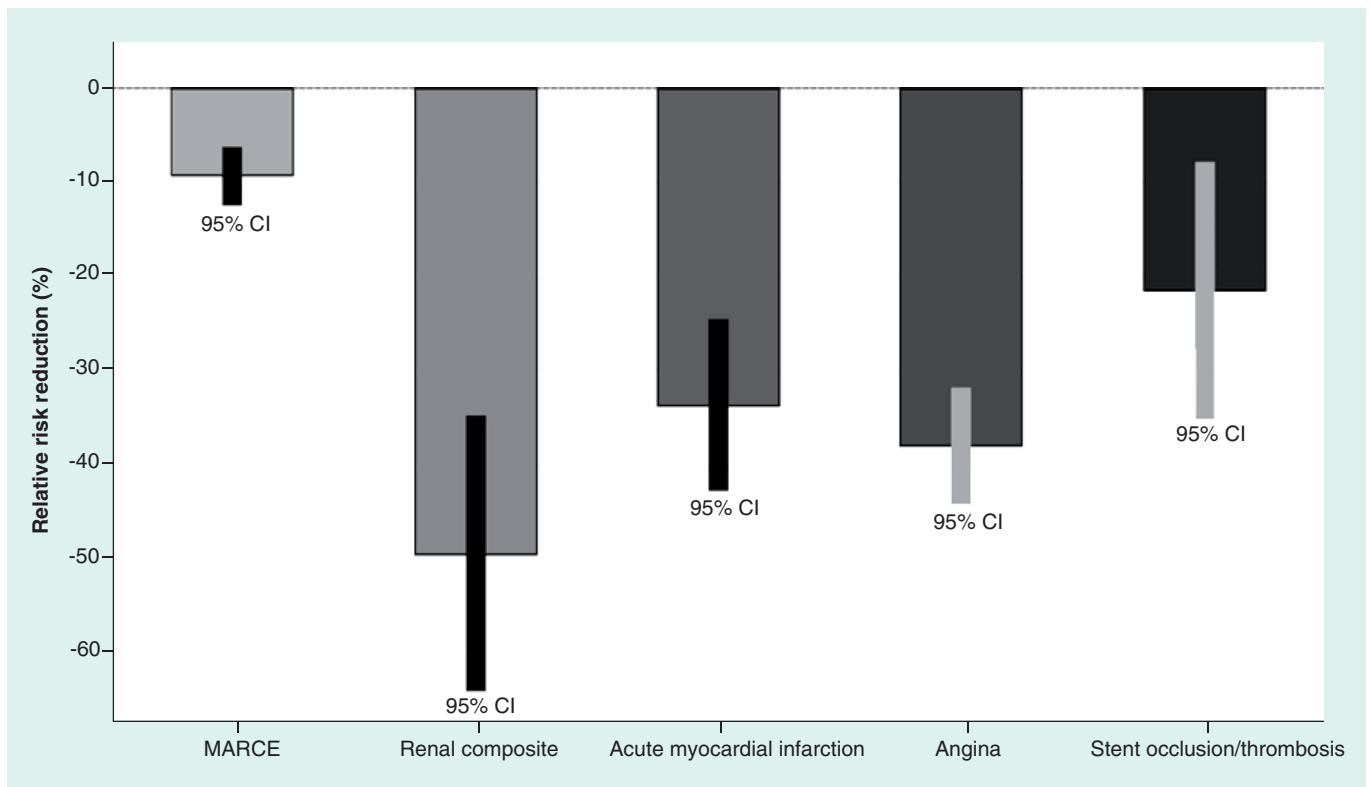


Figure 2. Relative risk of adverse events associated with iso-osmolar contrast media compared with low-osmolar contrast media. The fully saturated model included hospital fixed effects, year, procedure, patient demographics and patient comorbidities. The absolute risk reduction and the prevalence of each event were used to calculate the relative risk reduction, which is shown above. Prevalence of each event: MARCE (7.41%), renal composite (0.42%), acute myocardial infarction (1.06%), angina (2.13%) and stent occlusion/thrombosis (0.50%). Renal composite: Renal event that required dialysis, ICD-9 code 585.6 or 584.9 + 39.95. IOCM: Iso-osmolar contrast media; LOCM: Low-osmolar contrast media; MARCE: Major adverse renal and cardiovascular event.

Table 3, column 4, displays the fully saturated multivariable model with all of the covariate adjustments as stated above (hospital fixed effects, year, procedure type, patient demographics and patient comorbidities which includes severity of illness). CM volume was considered for model inclusion as the last step in the regression.

For patients with missing CM volume data, the median CM volume (200 ml) was imputed and outliers were removed. When CM volume was added to the model, there was very little to no change in the parameter estimates. Since the CM volume variable has significant amounts of missing data, represents the amount of CM volume charged, not actually administered and added little to no change in the coefficient estimates, it was decided to not include CM volume in the final model results.

Table 3 describes results for the primary outcome, MARCE, as well as the secondary outcomes: renal composite, AMI, angina, stent occlusion/thrombosis. The estimated regression coefficient reported represents the absolute risk reduction (ARR) when IOCM is compared with LOCM. The coefficient should be interpreted as the actual percentage point change in the adverse event rate.

In the fully adjusted model, inpatient percutaneous vascular intervention patients receiving IOCM versus LOCM had a 0.69 percentage point reduction (ARR) in the risk of a MARCE event. This ARR for MARCE as well as the ARR of components of MARCE are given in Table 3. As the additional variables are included in the model, MARCE events decrease until in the final model, with the addition of patient comorbidities, there is 0.69 percentage point less risk of a MARCE with IOCM in comparison to LOCM. The rate of MARCE was 7.41%, this translated into a 9.32% relative risk reduction per procedure with a number needed to treat of 145 to prevent one MARCE event. Administration of IOCM versus LOCM was associated with a 9% decrease in the overall MARCE rate, 50% decrease in the renal composite end point, 34% decrease in the risk for AMI, 38% decrease in the risk for angina and 21% decrease in the need for repeat stent implantation (Figure 2). As a sensitivity analysis, the patients with

a primary diagnosis of peripheral arterial disease (5.25%) were removed and the fully adjusted model results were confirmatory.

Discussion

In this present study of 333,533 visits, where patients were admitted to the hospital and underwent coronary, carotid or peripheral angiography and percutaneous intervention, approximately 30% received IOCM. Using models, which accounted for availability of IOCM, patient risk characteristics and other factors, IOCM use was associated with lower rates of MARCE. We also found individually lower postprocedure rates of renal events that required dialysis, acute myocardial infarction, angina and stent occlusion/thrombosis. These lower rates of MARCE when applied across the large number of angioplasty procedures done annually in the USA translate into clinically meaningful outcomes. In our analysis, we demonstrated the importance of accounting for breadth of clinical care variables. When simple models are used and all the determinants of CM are not considered, the use of IOCM appears to be falsely associated with higher rates of MARCE, which we believe is due to selection bias and confounding by indication.

Preprocedure assessment (e.g., by using the Mehran score for contrast nephropathy) and preventive action are important for reducing the risk for CI-AKI [29]. Precontrast administration of isotonic intravenous fluid, minimization of the volume of contrast [30] and administration of IOCM agents are all prudent actions. In our study, patients receiving IOCM compared with LOCM were older, sicker and more likely to be women. Patients who received IOCM were sicker as measured by the average Charlson Comorbidity Index Score, and had higher rates of diabetes with complications and renal disease. This suggests that treating physicians may preferentially administer IOCM to higher risk patients. Additionally, operators may select IOCM for perceived lower risks of major allergic complications or more tolerable symptoms during injection, particularly with peripheral procedures [31]. Despite their higher baseline risk, after adjusting for hospital fixed effects, patient demographics and comorbid conditions of the cohort, the use of IOCM was associated with fewer adverse events.

Chawla *et al.* introduced the composite end point of MARCE as the combination of MACE and MAKE [18]. Our study is the first large-scale effort to determine the impact of CM type on MARCE in hundreds of thousands of patients. Our results are supportive of more recent meta-analyses that used head-to-head trials comparing IOCM and LOCM where there were protocol-defined standardized time points for sampling serum creatinine, and thus more precise assessment of the primary outcome [12,16]. In these trials, the use of IOCM was associated with lower risk for CI-AKI. We demonstrated in a large sample of patients seeking care at hospitals in the USA, when model specifications are robust and confounding variables are adequately adjusted for, a favorable treatment effect for IOCM can be seen on hard clinical end points that make up the composite of MARCE.

Randomized controlled trials have long been the gold standard to generate efficacy and safety data; however, recently, payers are turning to real world data when there is a need to better understand the measurable impact of a particular intervention or therapy. Our data are consistent with the meta-analyses of intra-arterial injection of IOCM and LOCM where there were prespecified outcomes of AKI with measurement of serum creatinine [15,16]. Our data extend these findings to suggest that the extension of biochemical evidence of AKI is MARCE in the more severe cases. The use of real world data is becoming increasingly important to support clinical decision making and provide information and evidence to better support the value of an intervention in clinical practice [32].

Strengths & limitations

Strengths of this study include the use of a comprehensive data source and use of the hospital fixed-effect specification methodology that allowed control for time invariant within hospital variation that is otherwise unobservable in the choice of CM, such as hospital protocols specifying when to use IOCM or LOCM. The strength of the methods include the steps taken to control for unobservable factors, such as physician preference and internal protocols (including but not limited to hydration protocols), within the hospital that are used in determining the choice of IOCM or LOCM, in addition to observable factors.

The limitations of this study are those that are inherent in retrospective database analyses. The unit of inference was the visit and not the patient; thus, repeated procedures in the same patient may have influenced the results. The data source for this study was the premier database that represents 20% of all inpatient discharges in the USA; however, given its reliance on ICD-9 codes, the risk of coding errors can not be eliminated. A second limitation of this data source is that it does not track patients longitudinally. Thus, it was not possible to determine if events occurred after the patient was discharged. Due to the administrative nature of the database, lab values, vascular

access, bleeding and administration of intravenous fluids data were not available and thus remain as unaccounted confounders. Since actual volume of CM administered is not available in the dataset, a proxy variable based on the charge for CM was explored but not included in the final analysis. However, future studies should consider the volume of CM administered. Due to the lack of laboratory values, we could not define CI-AKI by serum creatinine levels, rather the outcome was defined by the ICD-9 code for CI-AKI which may underestimate the occurrence of this event.

Conclusion

It is important to control for both observable and unobservable time invariant within-hospital characteristics when assessing whether a difference exists in outcomes between IOCM versus LOCM. This large retrospective multicenter study showed that IOCM is being used in an older population with a greater burden of concomitant illnesses in comparison to LOCM. The use of IOCM was associated with a 0.69% ARR which translates into a 9.32% relative risk reduction of MARCE events compared with patients who received LOCM for inpatient angiography with percutaneous intervention.

Summary points

- Inpatient visits with a record of a primary procedure code for coronary or peripheral angioplasty from the premier database from 1 January 2008 through 30 September 2013 were analyzed.
- Angioplasty visits were stratified into two cohorts based on contrast media agents used: iso-osmolar contrast media (IOCM) (iodixanol) and low-osmolar contrast media (LOCM) (iohexol, ioversol, iopamidol, ioxaglate, ioxilan or iopromide).
- The outcome of interest was the major adverse renal and cardiovascular events (MARCE) composite end point, defined as renal failure with dialysis, acute kidney injury with or without dialysis, acute myocardial infarction, angina, stent occlusion/thrombosis, stroke, transient ischemic attack or death.
- Multivariable regression analysis was conducted using the hospital fixed-effects specification to assess the relationship between MARCE events and type of CM.
- A total of 333,533 primary inpatient angioplasty procedures in 357 hospitals met the study criteria for inclusion in this analysis.
- Patients who received IOCM were older (66.75 vs 63.82 years; $p < 0.0001$) and more likely to be in the 'extreme' category for both severity of illness (7.31 vs 5.00%; $p < 0.0001$) and mortality risk (6.35 vs 4.27%; $p < 0.0001$).
- Using models that accounted for availability of IOCM, patient risk characteristics and other factors, IOCM use was associated with lower rates of MARCE as well as lower postprocedure rates of renal events that required dialysis, acute myocardial infarction, angina and stent occlusion/thrombosis.
- In the fully adjusted model, which controlled for observable and unobservable time invariant within-hospital characteristics, administration of IOCM versus LOCM was associated with a 0.69% absolute and 9.32% relative risk reduction in MARCE rate.
- These results from a large retrospective database analysis are supportive of recent meta-analyses that used head-to-head trials comparing IOCM and LOCM.
- Despite higher baseline risk of patients given IOCM, after adjusting for hospital fixed effects, patient demographics and comorbid conditions of the cohort, the use of IOCM was associated with fewer adverse events.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2017-0052

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

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