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Is Intravenous Administration of Iodixanol Associated with Increased Risk of Acute Kidney Injury, Dialysis, or Mortality? A Propensity Score–adjusted Study[1]

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Purpose: To compare the rates of acute kidney injury (AKI), emergent dialysis, and short-term mortality between patients who underwent intravenous administration of the iso-osmolar contrast material (IOCM) iodixanol 320 and patients who underwent a noncontrast computed tomography (CT) examination.

Materials and Methods: Study design and implementation were overseen by an institutional review board and conformed to HIPAA guidelines on patient data integrity. All patients who underwent an iodixanol-enhanced (IOCM group) or a noncontrast (noncontrast group) CT examination from January 2003 to December 2014 were identified. Patients were subdivided into subgroups of those with stage 1–2 chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR], ≥ 60 mL/min/1.73 m^2), those with stage 3 CKD (eGFR, 30–59 mL/min/1.73 m^2), and those with stage 4–5 CKD (eGFR < 30 mL/min/1.73 m^2) and separately underwent propensity score stratification and matching. Rates of AKI, emergent dialysis, and mortality were compared between IOCM and noncontrast groups. Additional analyses incorporating intravenous fluid administration, including additional CT studies at other sites within a single institution, and a paired analysis of patients who underwent both IOCM and noncontrast CT studies during the study time frame, were also performed.

Results: A total of 5758 patients (1538 with stage 1–2 CKD, 2899 with stage 3 CKD, and 1321 with stage 4–5 CKD) were included in the study. After propensity score adjustment, rates of AKI, dialysis, and mortality were not significantly higher in the IOCM group compared with the noncontrast group for all CKD subgroups (AKI odds ratios [ORs], 0.74–0.91, P = .16–0.69; dialysis ORs, 0.74–2.00, P = .42–.76; mortality ORs, 0.98–1.24, P = .39–.88). Sensitivity analyses yielded similar results.

Conclusion: Among patients at the highest perceived risk of postcontrast AKI, intravenous administration of iodixanol for contrast material enhanced CT was not an independent risk factor for AKI, dialysis, or mortality.

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Online supplemental material is available for this article.

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Research reported in this study was supported by an investigator-initiated research grant from GE Healthcare (GE-012-102).The authors maintained control of the study data at all times.

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Postcontrast (PC) acute kidney injury (AKI), or the development of AKI after the administration of iodinated contrast material for imaging examinations and procedures, is a substantial concern for radiologists and ordering providers (1). Recent studies (2–6) have shown that the rate and severity of this complication have been exaggerated by prior uncontrolled studies. Several large retrospective propensity score–adjusted studies performed by our group found similar rates of PC-AKI, dialysis, and mortality between patients who underwent contrast material–enhanced computed tomography (CT) examinations and those who underwent noncontrast CT examinations, even in patients with poor renal function (baseline estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) in both groups (7–10). However, because of our institutional practices, most of the patients in these studies received the low-osmolar contrast material iohexol 300. A fraction of patients received the iso-osmolar contrast material (IOCM) iodixanol 320 because of their perceived higher risk of developing PC-AKI compared with iohexol recipients. To our knowledge, it is therefore unknown whether these higher-risk iodixanol recipients also have similar rates of poor outcomes after contrast material administration compared with clinically matched patients who undergo noncontrast CT.

The purpose of our study was therefore to compare the rates of PC-AKI, emergent dialysis, and short-term mortality between these higher-risk patients who were intravenously given the IOCM iodixanol and patients who underwent a noncontrast CT examination. Propensity score analysis, a method to minimize the confounders and selection bias inherent in retrospective studies, was used to match iodixanol recipients with control patients with similar acute and chronic clinical characteristics.

Advances in Knowledge

- Rates of acute kidney injury (AKI), dialysis, and mortality were not significantly higher in a cohort of patients who underwent an iodixanol-enhanced CT examination compared with propensity score–matched patients who underwent a noncontrast CT examination (AKI odds ratios [ORs], 0.74–0.91, P = .16–.69; dialysis ORs, 0.74–2.00, P = .42–.76; mortality ORs = 0.98–1.24, P = .39–.88).
- AKI rates were similar after iodixanol-enhanced CT and noncontrast CT within a subset of patients who underwent both types of examinations (Acute Kidney Injury Network definition: 9.9% for iso-osmolar contrast material [IOCM]-enhanced CT vs 17% noncontrast CT, P = .06; standard definition: 11% IOCM-enhanced CT vs 12% noncontrast CT, P = .88).

Materials and Methods

Study Design and Data Retrieval

Research reported in our study was financially supported by an investigator-initiated research grant from GE Healthcare. None of the authors are or have been employees of GE Healthcare. The authors maintained control of the study data and of the submitted manuscript at all times.

Study design and implementation for our retrospective study were overseen by our institutional review board and conformed with Health Insurance Portability and Accountability Act guidelines on patient data integrity. Only patients who had given approval for the use of their medical records for research purposes were included in our study. Clinical data in our electronic medical record were extracted by using both automated retrievals (DDQB; IBM, Armonk, NY) and manual chart review by one of the investigators (J.S.M.), as previously described (8,9). When performing chart review and manual data extraction, this investigator (J.S.M.) was blinded as to whether the patient underwent an iodixanol-enhanced or a noncontrast CT examination.

Study Population

From among the 15 423 total patients in the current study, 1538 were included in previous studies that examined outcomes in patients who underwent contrast-enhanced or noncontrast CT scanning (7–10). However, none of these prior studies specifically examined the effect of administration of a specific contrast material on clinical outcomes.

At our institution, ordering providers and radiologists have the choice of using iohexol or iodixanol for contrast-enhanced procedures and examinations. Institutional guidelines recommend that patients at particular risk of developing PC-AKI, including patients with greatly elevated baseline serum creatinine (SCr) levels or reduced eGFR and other risk factors, receive

Implication for Patient Care

- Among patients at highest perceived risk of postcontrast AKI, intravenous administration of iodixanol for contrast-enhanced CT was not an independent risk factor for AKI, dialysis, or mortality.

http://doi.org/10.1148/radiol.2017161573

Content codes: CT GU

Radiology 2017; 285:414–424

Abbreviations:
AKI = acute kidney injury
AKIN = Acute Kidney Injury Network
CKD = chronic kidney disease
eGFR = estimated glomerular filtration rate
IOCM = iso-osmolar contrast material
KDOQI = Kidney Disease Outcomes Quality Initiative
PC = postcontrast
SCr = serum creatinine

Author contributions:
Guarantor of integrity of entire study, J.S.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, J.S.M., R.J.M.; clinical studies, J.S.M., R.J.M., E.E.W.; statistical analysis, J.S.M.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

iodixanol instead of iohexol. Adult patients (≥18 years of age) were included if they *(a)* underwent an iodixanol-enhanced (IOCM group) or a noncontrast (noncontrast group) abdominal, pelvic, and thoracic CT examination from January 1, 2003, to December 30, 2014, at Mayo Clinic Rochester and *(b)* had at least two prescan (within 7 days prior) SCr results and at least one postscan (within 24–72 hours after) SCr result. Exclusion criteria were as follows: *(a)* patients currently undergoing dialysis, *(b)* patients without sufficient pre- and postscan SCr results, *(c)* patients missing any clinical data used to generate the propensity score model (Table 1), and *(d)* patients who were given additional contrast material within 14 days of the CT examination. Patients who underwent multiple CT examinations during the study time frame had only their last CT examination included in the analysis.

Baseline Renal Function

The mean SCr result in the 7 days prior to CT scanning was used to calculate baseline eGFR for each patient by using the Modification of Diet in Renal Disease equation according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, as previously described (7). Patients were categorized into the following subgroups: Those with an eGFR of 60 mL/min/1.73 m^2 or greater (CKD stage 1–2), those with an eGFR of 30–59 mL/min/1.73 m^2 (CKD stage 3), and those with an eGFR of less than 30 mL/min/1.73 m^2 (CKD stage 4–5), per the KDOQI guidelines for classification of CKD (11).

Outcome Variables

Study outcomes were PC-AKI, emergent dialysis, and death after CT examination. PC-AKI was defined as an increase in maximal observed SCr of either *(a)* 0.5 mg/dL or greater ("standard AKI criteria," chosen to standardize our results with those of prior studies that used this AKI cutoff) or *(b)* 0.3 mg/dL or greater or 50% or more over baseline (Acute Kidney Injury Network [AKIN] criteria, chosen to adhere to recent AKIN definitions of AKI [12]) in a 24–72-hour window after the CT examination. Cases of emergent dialysis and mortality in the 30 days after CT were identified as previously described (10).

Propensity Score Analysis

Generation of propensity scores, stratification by decile, and 1:*n* matching of patients between the IOCM and noncontrast groups were performed by J.S.M. using the R package MatchIt, as previously described (9). Stratification was performed in addition to matching to account for low sample sizes in certain subgroups. Nearest-neighbor (Greedy-type) matching without replacement was performed by using a caliper width of 0.15 standard deviation of the propensity score logit. All subgroups underwent 1:1 matching on the basis of propensity score, except for the CKD 4–5 subgroup, which underwent 1:3 (IOCM:noncontrast) matching because of the small number of patients in the IOCM group. Logistic regression models derived from the 32 variables listed in Table 1 were separately created for all eGFR subgroups.

Sensitivity Analysis: Inclusion of Intravenous Fluid Administration Data

The total amount of intravenous fluids given to patients 24 hours prior to CT examination was included as a covariate in the propensity score model described above. The amounts of intravenous fluids given to patients on the day of and 24 hours after the CT examination were not included in this model because these administrations took place after the decision to administer contrast material, potentially affecting the model result. A sensitivity analysis was instead performed by adding these two post-hoc covariates as adjustment covariables to a conditional logistic regression model after matching with prescan intravenous fluids and other Table 1 covariates.

Sensitivity Analysis: Incorporation of Additional CT Examinations Performed at Other Medical Centers

A sensitivity analysis was performed by including additional CT scans performed from January 1, 2010, to December 30, 2014, at all Mayo Clinic sites (Mayo Clinic Rochester, Mayo Clinic Health Systems, Mayo Clinic Arizona, Mayo Clinic Florida) to increase sample sizes and strengthen our findings. Only patients with renal insufficiency (baseline eGFR < 60 mL/min/1.73 m^2) were included in the analysis. Inclusion and exclusion criteria for the above studies were identical to those in the original analysis, except that patients who were undergoing dialysis could not be reliably identified and were therefore not excluded. Certain clinical variables (intensive care unit status, administered medications, intravenous fluid administration) were not easily retrievable from the electronic medical records of these sites and were not included in the propensity score model. Data on whether patients underwent emergent dialysis after CT scanning were also not retrievable and were not included in the outcomes analysis.

Sensitivity Analysis: Paired Analysis of Patients Who Underwent Both IOCM-enhanced and Noncontrast CT Examinations

A subset of patients was identified who underwent both an IOCM-enhanced and a noncontrast CT examination at all Mayo Clinic sites at least 14 days apart during the study time frame. Propensity scores were generated by J.S.M. for each paired scan event by using the same logistic model described above to account for small changes in baseline clinical characteristics and demographics (eg, age, new comorbidities) that might occur between the initial and subsequent examinations in the same patient. The rate of PC-AKI was compared between paired IOCM and noncontrast examinations by using the McNemar test, as previously described (9).

Statistical Analysis

Statistical analyses were performed by J.S.M. and R.J.M. using R (version 3.0.3, R Foundation for Statistical Computing, Vienna, Austria) (13). Continuous data were presented as medians with interquartile ranges, and categoric data were displayed as

Table 1

Demographics of Unadjusted and 1:1 Matched CKD Stage 1–2 Cohort

	Unadjusted Cohort			1:1 Propensity Score–matched Cohort		
Parameter	IOCM Group	Noncontrast Group	*P* Value	IOCM Group	Noncontrast Group	*P* Value
No. of examinations	637	901		476	476	
Age (y)*†	61 (50–72)	61 (46–72)	.65	61 (48–73)	63 (50–73)	.61
No. of women†	215 (34)	465 (52)	<.0001	193 (41)	191 (40)	.89
Caucasian race†	593 (93)	818 (91)	.11	441 (93)	438 (92)	.72
Admission type†			<.0001			.92
Inpatient	313 (49)	499 (55)		232 (49)	234 (49)	
Emergency room/inpatient	184 (29)	288 (32)		148 (31)	151 (32)	
Outpatient	140 (22)	114 (13)		96 (20)	91 (19)	
In ICU at time of examination†	102 (16)	69 (7.7)	<.0001	62 (13)	59 (12)	.77
Pre-existing comorbidities†						
Diabetes mellitus	250 (39)	253 (28)	<.0001	172 (36)	158 (33)	.31
Diabetic nephropathy	29 (4.6)	7 (0.8)	<.0001	9 (1.9)	6 (1.3)	.44
Hypertension	465 (73)	537 (60)	<.0001	325 (68)	322 (68)	.83
CKD	166 (26)	155 (17)	<.0001	104 (22)	98 (21)	.62
Multiple myeloma	27 (4.2)	13 (1.4)	.0007	13 (2.7)	11 (2.3)	.68
Congestive heart failure	117 (18)	169 (19)	.85	88 (18)	90 (19)	.87
Charlson comorbidity score*†	2 (1–5)	3 (1–6)	.0126	2 (1–6)	2 (1–5)	.86
Conditions within 7 days of examination†						
AKI	99 (16)	102 (11)	.0156	55 (12)	57 (12)	.84
Renal stone	9 (1.4)	50 (5.6)	<.0001	9 (1.9)	8 (1.7)	.81
Sepsis	65 (10)	131 (15)	.0120	53 (11)	42 (8.8)	.23
Prescribed nephrotoxic/nephromodulatory medication at time of examination†						
Antibiotics other than vancomycin	112 (18)	141 (16)	.31	78 (16)	75 (16)	.80
Vancomycin	116 (18)	123 (14)	.0151	79 (17)	77 (16)	.86
ACE inhibitors	138 (22)	126 (14)	<.0001	89 (19)	87 (18)	.87
ARBs	52 (8.2)	76 (8.4)	.85	38 (8.0)	40 (8.4)	.81
Chemotherapeutics	16 (2.5)	33 (3.7)	.21	15 (3.2)	13 (2.7)	.70
Cox-2 inhibitors	8 (1.3)	6 (0.7)	.23	5 (1.1)	5 (1.1)	.99
Loop diuretics	221 (35)	186 (21)	<.0001	142 (30)	135 (28)	.60
HCTZ	63 (9.9)	68 (7.6)	.10	40 (8.4)	39 (8.2)	.91
Immunosuppressants other than sirolimus	43 (6.8)	32 (3.6)	.0041	21 (4.4)	21 (4.4)	.99
Sirolimus	3 (0.5)	3 (0.3)	.67	3 (0.6)	3 (0.6)	.99
NSAIDs	39 (6.1)	109 (12)	<.0001	33 (6.9)	34 (7.1)	.90
Statins	225 (35)	225 (25)	<.0001	151 (32)	158 (33)	.61
Intravenous fluids administered around examination						
24 Hours before examination†	126 (20)	127 (14)	.0031	79 (17)	75 (16)	.72
Amount administered (mL)*†	1000 (538–1440)	840 (350–1000)	.0082	1000 (500–1320)	1000 (475–1250)	.55
Day of examination	202 (32)	266 (30)	.36	143 (30)	129 (27)	.32
Amount administered (mL)*	1000 (530–1561)	1000 (500–1355)	.0536	1000 (500–1630)	1000 (438–1400)	.13
24 Hours after examination	213 (33)	329 (37)	.21	160 (34)	154 (32)	.68
Amount administered (mL)*	1000 (638–1525)	1000 (640–1500)	.88	1000 (600–1538)	1000 (600–1604)	.78
Baseline eGFR*†	79 (67–100)	88 (74–109)	<.0001	83 (70–103)	85 (72–104)	.63
SCr stability prior to examination†			<.0001			.75
Stable	581 (91)	885 (98)		457 (96)	461 (97)	

Table 1 *(continues)*

Table 1 (continued)

Demographics of Unadjusted and 1:1 Matched CKD Stage 1–2 Cohort

	Unadjusted Cohort			1:1 Propensity Score–matched Cohort		
Parameter	IOCM Group	Noncontrast Group	*P* Value	IOCM Group	Noncontrast Group	*P* Value
Unstable-increasing	14 (2.2)	8 (0.9)		9 (1.9)	7 (1.5)	
Unstable-decreasing	42 (6.6)	8 (0.9)		10 (2.1)	8 (1.7)	
SCrΔ (maximum SCr − minimum SCr)*†	0.1 (0.1–0.2)	0.1 (0.1–0.2)	.0003	0.1 (0–0.2)	0.1 (0.1–0.2)	.67

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses. ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker, CKD = chronic kidney disease, cox-2 = cyclooxygenase 2, HCTZ = hydrochlorothiazide, ICU = intensive care unit, NSAID = nonsteroidal anti-inflammatory drug.

* Data are medians, with interquartile ranges in parentheses.

† Covariates included in the propensity score model.

relative frequencies (percentages). Clinical characteristic and outcome rate differences were compared between the IOCM and noncontrast groups prior to matching by using the Wilcoxon rank-sum test, Fisher exact test, or Pearson χ^2 test. The collective risk of each outcome following stratification by propensity score was determined by using Cochran-Mantel-Haenszel estimates. Clinical characteristic and outcome rate differences were compared between the IOCM and noncontrast groups after propensity score matching by using conditional logistic regression. $P < .05$ was considered to indicate a significant difference for most comparisons; however, a Bonferroni-corrected $P < .0125$ was considered to indicate significance when examining the four outcomes (AKI according to standard criteria, AKI according to AKIN criteria, dialysis, mortality).

Results

Study Population and Propensity Score Adjustment

A total of 5758 patients (2348 women, 3410 men; 1538 CKD stage 1–2; 2899 CKD stage 3; 1321 CKD stage 4–5) were included in the study (Fig E1 [online]). Prior to propensity score adjustment, patients in the IOCM group and patients in the noncontrast group had significant differences in numerous clinical variables (Tables 1–3). Patients who underwent IOCM-enhanced scanning had significantly higher rates of diabetes (stage 1–2, 250 of 637 [39%] vs 253 of 901 [28%], $P < .0001$; stage 3, 520 of 1234 [42%] vs 592 of 1665 [36%], $P = .0003$), hypertension (stage 1–2, 465 of 637 [73%] vs 537 of 901 [60%], $P < .0001$; stage 3, 1013 of 1234 [82%] vs 1163 of 1665 [70%], $P < .0001$; stage 4–5, 83 of 90 [92%] vs 1018 of 1231 [83%], $P = .0192$), and CKD (stage 1–2, 166 of 637 [26%] vs 155 of 902 [17%], $P < .0001$; stage 3, 889 of 1234 [72%] vs 1007 of 1665 [60%], $P = .0003$); and significantly higher use of medications such as vancomycin (stage 1–2, $P = .0151$; stage 3, $P < .0001$), loop diuretics (stage 1–2, $P < .0001$; stage 3, $P = .0015$), and statins (stage 1–2 $P < .0001$, stage 3 $P < .0001$) compared with patients who underwent noncontrast CT examinations.

Propensity score matching (1:*n*) yielded cohorts of 952 patients in the CKD stage 1–2 subgroup of patients undergoing CT scanning (476 in the IOCM group and 476 in the noncontrast group), 1700 patients in the CKD stage 3 subgroup (850 in the IOCM group and 850 in the noncontrast group), and 274 patients in the CKD stage 4–5 subgroup (1:3 matching; 76 in the IOCM group and 198 in the noncontrast group) (Tables 1–3). Propensity score matching removed significant differences in all model covariates between the IOCM and noncontrast groups in all eGFR subgroups.

Outcome Rates after Propensity Score Adjustment

Outcomes before propensity score adjustment and after propensity score stratification and matching are shown in Tables 4–6. After stratification, PC-AKI rates using either cutoff value were similar between the IOCM and noncontrast groups in all CKD subgroups. Similar PC-AKI rates were also observed after matching of the IOCM and noncontrast groups. Emergent dialysis rates were low (0.8% in the CKD 1–2 subgroup to 2.0% in the CKD 4–5 subgroup) and were similar between the IOCM and noncontrast groups after propensity score stratification and matching. Short-term mortality rates were also similar between the IOCM and noncontrast groups after propensity score adjustment.

Sensitivity Analysis: Inclusion of Intravenous Fluid Administration Data

Data regarding intravenous fluids administered on the day of or on the day after CT scanning were included in a separate sensitivity analysis. The percentage of patients who were given intravenous fluids and the amount of intravenous fluids administered in the day before, day of, and day after CT scanning were similar in the propensity score–matched IOCM and noncontrast groups in all CKD subgroups. Outcome rates remained similar between the IOCM and noncontrast groups after incorporation of intravenous fluid administration data on the day of and the day after CT scanning (Tables E1–E3 [online]).

Table 2

Demographics of Unadjusted and 1:1 Matched CKD Stage 3 Cohort

	Unadjusted Cohort			1:1 Propensity Score–matched Cohort		
Parameter	IOCM Group	Noncontrast Group	*P* Value	IOCM Group	Noncontrast Group	*P* Value
No. of examinations	1234	1665		850	850	
Age (y)*	72 (63–80)	67 (58–77)	<.0001	70 (60–80)	69 (60–80)	.72
No. of women	416 (34)	615 (37)	.07	310 (36)	313 (37)	.88
Caucasian race	1189 (96)	1547 (93)	<.0001	814 (96)	807 (95)	.42
Admission type			<.0001			.48
Inpatient	544 (44)	1224 (74)		490 (58)	510 (60)	
Emergency room/inpatient	390 (32)	326 (20)		245 (29)	235 (28)	
Outpatient	300 (24)	115 (6.9)		115 (14)	105 (12)	
In ICU at time of examination	188 (15)	386 (23)	<.0001	159 (19)	157 (18)	.90
Pre-existing comorbidities						
Diabetes mellitus	520 (42)	592 (36)	.0003	351 (41)	344 (40)	.73
Diabetic nephropathy	129 (10)	116 (7.0)	.0008	84 (9.9)	75 (8.8)	.45
Hypertension	1013 (82)	1163 (70)	<.0001	660 (78)	643 (76)	.30
CKD	889 (72)	1007 (60)	<.0001	582 (68)	594 (70)	.52
Multiple myeloma	15 (1.2)	49 (2.9)	.0017	14 (1.7)	17 (2.0)	.59
Congestive heart failure	414 (34)	564 (34)	.86	301 (35)	280 (33)	.30
Charlson comorbidity score*	4 (2–7)	5 (2–7)	<.0001	4 (2–8)	4 (2–7)	.73
Conditions within 7 days of examination						
AKI	363 (29)	627 (38)	<.0001	280 (33)	279 (33)	.96
Renal stone	28 (2.3)	106 (6.4)	<.0001	24 (2.8)	29 (3.4)	.48
Sepsis	98 (7.9)	154 (9.3)	.22	78 (9.2)	74 (8.7)	.73
Prescribed nephrotoxic/nephromodulatory medication at time of examination						
Antibiotics other than vancomycin	167 (14)	321 (19)	<.0001	138 (16)	140 (16)	.89
Vancomycin	183 (15)	341 (20)	<.0001	151 (18)	169 (20)	.27
ACE inhibitors	403 (33)	338 (20)	<.0001	259 (30)	234 (28)	.17
ARBs	159 (13)	139 (8.4)	<.0001	96 (11)	92 (11)	.76
Chemotherapeutics	31 (2.5)	29 (1.7)	.15	22 (2.6)	21 (2.5)	.88
Cox-2 inhibitors	19 (1.5)	10 (0.6)	.0120	10 (1.2)	8 (0.9)	.64
Loop diuretics	545 (44)	638 (38)	.0015	373 (44)	361 (42)	.56
HCTZ	183 (15)	118 (7.1)	<.0001	93 (11)	87 (10)	.63
Immunosuppressants other than sirolimus	81 (6.6)	207 (12)	<.0001	69 (8.1)	80 (9.4)	.33
Sirolimus	15 (1.2)	11 (0.7)	.12	11 (1.3)	9 (1.1)	.66
NSAIDs	76 (6.2)	66 (4.0)	.0068	47 (5.5)	44 (5.2)	.75
Statins	553 (45)	583 (35)	<.0001	369 (43)	353 (42)	.44
Intravenous fluids administered around examination						
24 Hours before examination	203 (16)	367 (22)	.0002	166 (20)	166 (20)	.99
Amount administered (mL)*	1000 (500–1500)	1000 (500–1500	.95	1000 (450–1500)	1000 (588–1308)	.82
Day of examination	356 (29)	477 (29)	.91	273 (32)	253 (30)	.28
Amount administered (mL)*	1000 (629–1600)	1000 (600–1550)	.60	1000 (638–1600)	1000 (800–1583)	.52
24 Hours after examination	364 (30)	473 (28)	.52	265 (31)	237 (28)	.13
Amount administered (mL)*	1008 (760–1721)	1000 (500–1563)	.0010	1050 (787–1700)	1000 (600–1600)	.0071
Baseline eGFR*	44 (39–50)	43 (36–50)	<.0001	44 (38–50)	44 (37–51)	.99
SCr stability prior to examination			<.0001			.81
Stable	1044 (85)	1199 (72)		693 (82)	703 (83)	
Unstable-increasing	63 (5.1)	237 (14)		55 (6.5)	52 (6.1)	
Unstable-decreasing	127 (10)	229 (14)		102 (12)	95 (11)	
SCrΔ (maximum SCr − minimum SCr)*	0.2 (0.1–0.3)	0.2 (0.1–0.4)	.28	0.2 (0.1–0.3)	0.2 (0.1–0.3)	.43

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses. ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker, cox-2 = cyclooxygenase 2, HCTZ = hydrochlorothiazide, ICU = intensive care unit, NSAID = nonsteroidal anti-inflammatory drug.

* Data are medians, with interquartile ranges in parentheses.

Table 3

Demographics of Unadjusted and 1:3 Matched CKD Stage 4–5 Cohort

	Unadjusted Cohort			1:3 Propensity Score–matched Cohort		
Parameter	IOCM Group	Noncontrast Group	*P* Value	IOCM Group	Noncontrast Group	*P* Value
No. of examinations	90	1231		76	198	
Age (y)*	74 (63–82)	67 (56–78)	.0001	73 (62–82)	72 (62–82)	.75
No. of women	64 (71)	573 (47)	<.0001	51 (67)	134 (68)	.78
Caucasian race	86 (96)	1133 (92)	.23	73 (96)	185 (93)	.71
Admission type			<.0001			.62
Inpatient	51 (57)	944 (77)		49 (64)	133 (67)	
Emergency room/inpatient	27 (30)	232 (19)		21 (28)	46 (23)	
Outpatient	12 (13)	55 (4.5)		6 (7.9)	19 (9.6)	
In ICU at time of examination	22 (24)	254 (21)	.39	21 (28)	53 (27)	.72
Pre-existing comorbidities						
Diabetes mellitus	43 (48)	470 (38)	.07	37 (49)	101 (51)	.71
Diabetic nephropathy	16 (18)	137 (11)	.0571	14 (18)	36 (18)	.86
Hypertension	83 (92)	1018 (83)	.0192	70 (92)	180 (91)	.70
CKD	70 (78)	916 (74)	.48	59 (78)	144 (73)	.71
Multiple myeloma	4 (4.4)	55 (4.5)	.99	3 (4.0)	8 (4.0)	.80
Congestive heart failure	41 (46)	439 (36)	.0596	35 (46)	81 (41)	.58
Charlson comorbidity score*	4 (2–6)	5 (3–8)	.0005	4 (3–6)	4 (2–6)	.90
Conditions within 7 days of examination						
AKI	47 (52)	947 (77)	<.0001	47 (62)	134 (68)	.53
Renal stone	0	54 (4.4)	.0425	0	0	—
Sepsis	14 (16)	253 (21)	.25	14 (18)	39 (20)	.83
Prescribed nephrotoxic/ nephromodulatory medication at time of examination						
Antibiotics other than vancomycin	12 (13)	203 (16)	.43	11 (14)	32 (16)	.25
Vancomycin	15 (17)	238 (19)	.53	15 (20)	40 (20)	.82
ACE inhibitors	24 (27)	335 (27)	.91	20 (26)	59 (30)	.72
ARBs	13 (14)	163 (13)	.75	12 (16)	29 (15)	.96
Chemotherapeutics	5 (5.6)	25 (2.0)	.0303	3 (4.0)	6 (3.0)	.88
Cox-2 inhibitors	1 (1.1)	18 (1.5)	.79	1 (1.3)	2 (1.0)	.76
Loop diuretics	52 (58)	675 (55)	.59	47 (62)	110 (56)	.72
HCTZ	12 (13)	124 (10)	.33	11 (14)	30 (15)	.88
Immunosuppressants other than sirolimus	4 (4.4)	138 (11)	.0455	4 (5.3)	13 (6.6)	.87
Sirolimus	0	15 (1.2)	.29	0	0	…
NSAIDs	4 (4.4)	59 (4.8)	.88	3 (4.0)	9 (4.6)	.98
Statins	42 (47)	502 (41)	.27	34 (45)	93 (47)	.41
Intravenous fluids administered around examination						
24 Hours before examination	10 (11)	323 (26)	.0010	10 (13)	30 (15)	.65
Amount administered (mL)*	816 (500–1969)	1000 (557–1600)	.61	816 (500–1969)	1000 (311–1505)	.78
Day of examination	19 (21)	392 (32)	.0337	15 (20)	42 (21)	.89
Amount administered (mL)*	945 (420–1000)	1000 (700–1545)	.0247	975 (420–1000)	1000 (681–1525)	.67
24 Hours after examination	15 (17)	402 (33)	.0016	13 (17)	51 (26)	.76
Amount administered (mL)*	1387 (850–1700)	1000 (591–1650)	.42	1387 (925–1800)	1075 (740–1600)	.54
Baseline eGFR*	26 (22–28)	21 (15–25)	<.0001	25 (21–28)	25 (21–27)	.80
SCr stability prior to examination			.0203			.99
Stable	49 (54)	539 (44)		40 (53)	106 (54)	
Unstable-increasing	26 (39)	318 (26)		21 (28)	52 (26)	
Unstable-decreasing	15 (17)	374 (30)		15 (20)	40 (20)	
SCrΔ (maximum SCr − minimum SCr)*	0.4 (0.2–0.9)	0.5 (0.3–1.1)	.0555	0.4 (0.2–0.9)	0.4 (0.2–0.8)	.87

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses. ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker, cox-2 = cyclooxygenase 2, HCTZ = hydrochlorothiazide, ICU = intensive care unit, NSAID = nonsteroidal anti-inflammatory drug.

* Data are medians, with interquartile ranges in parentheses.

Table 4

CKD Stage 1–2 Cohort Outcomes after Propensity Score Analysis

Parameter	IOCM Group	Noncontrast Group	Odds Ratio*	*P* Value
Unadjusted	637	901		
PC-AKI				
≥0.3 mg/dL or ≥ 50% SCr	57 (9.0)	83 (9.2)	0.97 (0.68, 1.38)	.86
≥0.5 mg/dL SCr	28 (4.4)	37 (4.1)	1.07 (0.65, 1.77)	.78
Dialysis within 30 days after scanning	6 (0.9)	4 (0.4)	2.13 (0.60, 7.59)	.23
Death within 30 days after scanning	52 (8.2)	59 (6.6)	1.27 (0.86, 1.87)	.23
Stratified	637	901		
PC-AKI				
≥0.3 mg/dL or ≥ 50% SCr	…	…	0.78 (0.52, 1.18)	.28
≥0.5 mg/dL SCr	…	…	0.76 (0.42, 1.37)	.45
Dialysis within 30 days after scanning	…	…	1.75 (0.45, 6.76)	.63
Death within 30 days after scanning	…	…	1.40 (0.91, 2.15)	.13
1:1 Matched	476	476		
PC-AKI				
≥0.3 mg/dL or ≥ 50% SCr	37 (7.8)	38 (10)	0.74 (0.46, 1.17)	.20
≥0.5 mg/dL SCr	18 (3.8)	22 (4.6)	0.81 (0.43, 1.54)	.52
Dialysis within 30 days after scanning	4 (0.8)	2 (0.4)	2.00 (0.37, 10.9)	.42
Death within 30 days after scanning	39 (8.2)	32 (6.7)	1.24 (0.76, 2.03)	.39

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

* Odds in IOCM group versus noncontrast group. Data in parentheses are 95% confidence intervals.

Sensitivity Analysis: Inclusion of CT Examinations Performed at Additional Medical Centers

A total of 13 885 patients with renal insufficiency (5601 women, 8284 men; 9715 CKD stage 3, 4170 CKD stage 4–5) were identified from all participating medical centers (Fig E2, Tables E4 and E5 [online]). Propensity score adjustment removed all significant differences in most clinical covariates between the IOCM and noncontrast groups. After adjustment, PC-AKI and dialysis rates were again similar between CKD stage 3 and CKD stage 4–5 IOCM and noncontrast groups (Tables E6 and E7 [online]).

Paired Analysis of Patients Who Underwent Both IOCM-enhanced and Noncontrast CT Examinations

A total of 677 patients were identified who underwent at least one IOCM-enhanced CT examination and one noncontrast CT examination during the study period. Propensity score matching and adjustment to identify patients and examinations with similar clinical characteristics at the time of both examinations resulted in a cohort of 181 patients (Table E8 [online]). A small percentage of noncontrast CT examinations (14%, n = 25) were specifically ordered instead of a contrast-enhanced CT examination because of the patient's poor renal function. The percentage of patients who experienced PC-AKI after only their IOCM-enhanced CT examinations was not higher than the percentage of patients who experienced PC-AKI after only their noncontrast CT examinations (Fig E3 [online]) (AKIN definition: 9.9% IOCM vs 17% noncontrast, P = .06; standard definition: 11% IOCM vs 12% noncontrast, P = .88).

Discussion

Our large retrospective propensity score–adjusted study demonstrated no increased risk of PC-AKI, dialysis, or mortality between patients who underwent an iodixanol-enhanced CT examination and those who underwent a noncontrast CT examination. This finding was observed irrespective of patient baseline renal function, after accounting for intravenous fluid administration, and after incorporating patients and clinical practices at other sites within our institution. Furthermore, the rate of PC-AKI was similar after iodixanol-enhanced CT examinations and noncontrast CT examinations within a subset of patients who underwent both types of examinations. This paired analysis enabled the comparison of outcomes after both types of examinations within the same patient, essentially removing the selection bias present in retrospective studies of causality. Among patients at highest perceived risk of PC-AKI, intravenous administration of iodixanol for contrast-enhanced CT was not an independent risk factor for AKI, dialysis, or mortality.

Our observation that the risks of PC-AKI, dialysis, and mortality are similar between iodixanol recipients and control patients are consistent with results of prior retrospective propensity score–adjusted studies that compared contrast material recipients with control patients (7–10,14,15). The majority of patients in these prior retrospective studies, as well as in prior PC-AKI prospective studies and retrospective studies that did not use propensity score adjustment, were given low- or high-osmolality contrast material. Our current study expands on these prior findings by specifically examining the risks associated with the administration of iodixanol in a cohort at high risk of developing PC-AKI.

Our institutional guidelines recommend use of the IOCM iodixanol for patients at high risk of developing PC-AKI, including patients with greatly elevated baseline SCr levels, reduced eGFR, and other risk factors, in lieu of the use of our standard low-osmolar contrast

Table 5

CKD Stage 3 Cohort Outcomes after Propensity Score Analysis

Parameter	IOCM Group	Noncontrast Group	Odds Ratio*	*P* Value
Unadjusted	1234	1665		
PC-AKI				
≥0.3 mg/dL or ≥ 50% SCr	185 (15)	284 (17)	0.86 (0.70, 1.05)	.14
≥0.5 mg/dL SCr	87 (7.1)	133 (8.0)	0.87 (0.66, 1.16)	.35
Dialysis within 30 days after scanning	7 (0.6)	25 (1.5)	0.37 (0.16, 0.87)	.0173
Death within 30 days after scanning	119 (9.6)	208 (12)	0.75 (0.59, 0.95)	.0165
Stratified	1234	1665		
PC-AKI				
≥0.3 mg/dL or ≥ 50% SCr	…	…	0.84 (0.67, 1.06)	.16
≥0.5 mg/dL SCr	…	…	0.89 (0.65, 1.23)	.53
Dialysis within 30 days after scanning	…	…	0.86 (0.32, 2.26)	.94
Death within 30 days after scanning	…	…	1.10 (0.85, 1.44)	.50
1:1 Matched	850	850		
PC-AKI				
≥0.3 mg/dL or ≥ 50% SCr	129 (15)	150 (18)	0.83 (0.64, 1.08)	.16
≥0.5 mg/dL SCr	61 (7.2)	67 (7.9)	0.91 (0.64, 1.29)	.59
Dialysis within 30 days after scanning	7 (0.8)	5 (0.6)	1.40 (0.44, 4.42)	.57
Death within 30 days after scanning	99 (12)	101 (12)	0.98 (0.73, 1.31)	.88

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

* Odds in IOCM group versus noncontrast group. Data in parentheses are 95% confidence intervals.

material, iohexol, and these policies are adhered to well by ordering providers. The purpose of our study was not to specifically compare PC-AKI rates between iodixanol and other low-osmolar contrast materials, because numerous prior studies have performed this comparison (16–21). Instead, we focused on a patient cohort that we believe was at higher perceived risk of PC-AKI because of the decision to administer iodixanol instead of iohexol. Patients in our prior studies, which predominantly involved iohexol recipients, had fewer chronic and acute illnesses (ie, in a postpropensity score match stage 3 predominantly iohexol cohort [8] vs the iodixanol cohort, the CKD rate was 30% vs 68% and the rate of being in the intensive care unit [ICU] was 15% vs 19%; in a postpropensity score match stage 4–5 predominantly iohexol cohort [8] vs the iodixanol cohort, the CKD rate was 48% vs 78% and the rate of being in the ICU was 18% vs 28%) and were therefore at lower risk of developing PC-AKI than patients in the iodixanol cohort in our current study (7–10). The higher overall predisposition to AKI in the current cohort did not translate into an increased risk of PC-AKI or related outcomes after intravenous administration of iodixanol compared with the risk in matched control patients. Although iodixanol is more expensive than iohexol, we sought to provide guidance to ordering providers and radiologists regarding the safety of this contrast material, as the incremental difference in cost between contrast materials is small relative to the overall cost of care.

Although we did not detect any significant differences in post-CT outcomes between contrast exposure groups after propensity score adjustment, several of our CKD subgroup analyses were limited by small sample sizes because of the small number of patients who received iodixanol. In an effort to determine if these sample size limitations precluded our ability to detect meaningful differences in clinical outcomes, we performed a post-hoc assessment of the detectable effect size. Using the confidence interval (CI) as an assessment of the precision of the estimated effect and the largest upper confidence limit as a conservative estimate of the smallest significant difference between the contrast and noncontrast groups that could be detected by our study (22–24), we found that we could detect differences in AKIN criteria PC-AKI of at least 1.5% among patients with stage 1–2 CKD (assuming PC-AKI rate = 10%; upper CI limit = 1.17), of at least 1.2% among patients with stage 3 CKD (assuming PC-AKI rate = 18%; upper CI limit = 1.08), and of 10.5% among patients with stage 4–5 CKD (assuming PC-AKI rate = 25%; upper CI limit = 1.65). Because the magnitude of the detectable differences in PC-AKI among patients with stage 1–3 CKD was smaller than the reported rates of PC-AKI in the literature, the sample size and precision of the odds ratio estimates for our study appear to be sufficient to make meaningful interpretations of the results among patients with stage 1–3 CKD. Although the smallest detectable differences among patients with stage 4–5 CKD are more limited by sample size, the published rates of PC-AKI in such groups ranges from 14% to 36% (7,14), suggesting that even this subset sample size, while not optimal, is sufficient to detect a clinically meaningful difference. However, larger studies focused on patients with stage 4–5 CKD are needed to better understand the risk of contrast material administration in this population, as such patients are underrepresented in our study, and the clinical decision algorithm to administer iodixanol out of medical necessity and urgency (assuming most providers would otherwise be unlikely to administer iodinated contrast material to this subpopulation) may be different

Table 6

CKD Stage 4–5 Cohort Outcomes after Propensity Score Analysis

Parameter	IOCM Group	Noncontrast Group	Odds Ratio*	*P* Value
Unadjusted	90	1231		
PC-AKI				
≥0.3 mg/dL or ≥ 50% SCr	14 (16)	347 (28)	0.47 (0.26, 0.84)	.0094
≥0.5 mg/dL SCr	9 (10)	264 (21)	0.41 (0.20, 0.82)	.0096
Dialysis within 30 days after scanning	1 (1.1)	63 (5.1)	0.21 (0.03, 1.52)	.09
Death within 30 days after scanning	19 (21)	195 (16)	1.42 (0.84, 2.41)	.19
Stratified	90	1231		
PC-AKI				
≥0.3 mg/dL or ≥ 50% SCr	…	…	0.51 (0.28, 0.93)	.0362
≥0.5 mg/dL SCr	…	…	0.40 (0.19, 0.83)	.0157
Dialysis within 30 days after scanning	…	…	0.80 (0.10, 6.18)	.83
Death within 30 days after scanning	…	…	2.01 (1.11, 3.64)	.0311
1:1 Matched	76	198		
PC-AKI				
≥0.3 mg/dL or ≥ 50% SCr	13 (17)	49 (25)	0.88 (0.47, 1.65)	.69
≥0.5 mg/dL SCr	8 (11)	42 (21)	0.81 (0.38, 1.70)	.58
Dialysis within 30 days after scanning	1 (1.3)	4 (2.0)	0.74 (0.10, 5.26)	.76
Death within 30 days after scanning	16 (21)	24 (12)	1.15 (0.63, 2.09)	.65

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

* Odds in IOCM group versus noncontrast group. Data in parentheses are 95% confidence intervals.

when compared with that in other populations.

Our study had several other limitations. First, propensity score analysis can account only for potential confounders that are included in the model. Our findings of similar risks after IOCM-enhanced CT scanning and noncontrast CT scanning correlate with results of prior randomized controlled trials and retrospective propensity score–adjusted studies. However, confounders may have remained that could have affected our results. Clinician intuition and preventative measures such as waiting to administer contrast material until patients were in a less-acute state cannot be determined from retrospective studies and were not included in our model. Second, only patients with sufficient pre- and postscan SCr results were included in our study, creating a cohort consisting mostly of inpatients. However, because inpatient populations are typically more acutely ill than outpatient populations, this bias increases the likelihood of observing PC-AKI. We were unable to assess how many patients with PC-AKI were excluded from this study, because PC-AKI could not be diagnosed in patients with insufficient SCr results. Additional PC-AKI studies focused specifically on patients with poor renal function are needed. Third, the median age of this cohort was high (70 years), limiting the generalizability of our findings in younger patients. However, we have no reason to suspect that our results would be substantially affected by patient age. Fourth, dynamic data such as changes in medication immediately prior to CT scanning are difficult to capture retrospectively; however, it is unlikely that this limitation would have been substantially different between the contrast and noncontrast groups. Fifth, we did not account for contrast material dose in our study. Finally, although we stratified patients by KDOQI CKD stage eGFR cutoffs, it is likely that a percentage of patients were classified into renal insufficiency subgroups because of acute or subacute changes in renal function instead of actual CKD.

In conclusion, among patients at highest perceived risk of PC-AKI, intravenous administration of iodixanol for contrast-enhanced CT was not associated with acute kidney injury, dialysis, or mortality.

Disclosures of Conflicts of Interest: J.S.M. Activities related to the present article: has an investigator-initiated research grant with GE Healthcare. Activities not related to the present article: has investigator-initiated research grants with GE Healthcare for contrast-induced nephropathy and gadolinium deposition studies independent of the current manuscript. Other relationships: disclosed no relevant relationships. **R.J.M.** disclosed no relevant relationships. **E.E.W.** Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: has investigator-initiated research grants with GE Healthcare for contrast-induced nephropathy studies independent of the current manuscript. Other relationships: disclosed no relevant relationships. **D.F.K.** Activities related to the present article: received funding for data analysis from GE Healthcare. Activities not related to the present article: is a member of the cost-effectiveness board of GE Healthcare; is a consultant on clinical trials planning for GE Healthcare; has grants or grants pending for preclinical and clinical research from GE Healthcare; has investigator-initiated research grants with GE Healthcare for contrast-induced nephropathy studies independent of the current manuscript. Other relationships: disclosed no relevant relationships.

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