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ORIGINAL RESEARCH

Risk of Worsening Renal Function Following Repeated Exposures to Contrast Media During Percutaneous Coronary Interventions

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BACKGROUND: Multiple contrast media exposures are common, but their cumulative effect on renal function is unknown. We aimed to investigate the renal consequences of repeated exposures to contrast media with coronary interventions.

METHODS AND RESULTS: We studied 2942 patients who underwent between 1 and 9 procedures. The primary end point was a persistent creatinine increase of ≥50% above baseline at ≥90 days after the last procedure. The effect of cumulative contrast media dose was assessed using Cox models, with cumulative exposure as a time-dependent variable, and propensity score matching. The primary end point occurred in 190 patients (6.5%), with 6.1%, 6.8%, and 6.2% of patients with 1, 2 or 3, and ≥4 procedures, respectively (P=0.75). In the multivariable Cox model, baseline renal function, diabetes, anemia, acute coronary syndrome, and heart failure were independent predictors of the primary end point (all P≤0.01), whereas cumulative contrast dose was not (hazard ratio [HR], 1.29 [95% CI, 0.89–1.88] for the fourth contrast quartile [>509 mL] versus first contrast quartile [<233 mL]). Propensity score matching yielded 384 patient pairs with similar characteristics and either 1 or 2 to 9 contrast exposures (median cumulative dose, 160 and 480 mL, respectively). Despite large differences in the cumulative contrast exposure, there were similar rates of the primary end points (7.3% versus 6.3%, respectively; HR, 0.76 [95% CI, 0.44–1.32]).

CONCLUSIONS: In patients with multiple exposures to contrast media, worsening of renal function over time is associated with known risk factors for the progression of kidney disease but not with cumulative contrast volume.

Key Words: acute kidney injury ■ contrast media ■ contrast-induced nephropathy

Contrast-associated acute kidney injury (CA-AKI) occurs in 1% to 3% in patients undergoing elective percutaneous coronary intervention (PCI),[1,2] and increases to 10% to 16% in patients undergoing PCI in the setting of an acute coronary syndrome.[3–5] CA-AKI assumes greater importance with increasing use of invasive coronary procedures for the diagnosis and treatment of coronary artery disease. However, the causal link between contrast media (CM) exposure and renal injury remains uncertain.[6–12]

Contrast-induced nephrotoxicity is considered an important cause of hospital-acquired renal failure.[13,14] However, most cases of CA-AKI manifest as mild transient impairment of renal function,[13] with transient decline in renal function and recovery typically beginning within 3 to 5 days. After 1 to 3 weeks, serum creatinine usually returns to baseline values or to a new baseline.[13] Some patients, however, have persistent decline in renal function[15] and subsequent progression to chronic kidney disease (CKD) and dialysis.[16]

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CLINICAL PERSPECTIVE

What Is New?

- The effect of contrast agents on the kidney is classically modeled as an acute insult but fails to consider the common scenario of repeated exposures to contrast media (CM) that occur over months or years.
- The current study of patients undergoing repeated CM exposures and propensity score–matched patients with a single CM exposure demonstrates similar rates of long-term worsening renal function despite large differences in the cumulative burden of CM exposure.
- Furthermore, contrast-associated acute kidney injury occurring shortly after CM administration accounts for a small proportion of the cases of long-term worsening renal function.

What Are the Clinical Implications?

- Multiple exposures to CM, as occurs with repeated revascularization procedures are not associated with worsening of renal function over time.
- These finding are clinically relevant and reassuring with regard to the common scenario of repetitive CM exposure and other contrast-enhanced imaging studies.
- The lack of dose-effect relationship is an important consideration against a potential causal relationship between CM exposure and chronic renal dysfunction.

Nonstandard Abbreviations and Acronyms

CA-AKI	contrast-associated acute kidney injury
CM	contrast media

The effect of contrast agents on the kidney is classically modeled as an acute insult, where contrast exposure leads to an acute increase in serum creatinine over a period of few days.[17] This analytic approach, however, fails to consider the common scenario of repeated exposures to CM that occur over months or years in many patients. Indeed, a substantial proportion of patients with coronary disease require more than one, and sometimes multiple, revascularization procedures,[18,19] resulting in repeated exposure to CM. Whether high cumulative doses of CM contribute to progressive long-term renal dysfunction is not known. In the present study, we sought to investigate the potential renal consequences of repeated exposures to CM during diagnostic or coronary interventions.

METHODS

Patients

Patients were identified from the Rambam Medical Center interventional database. The study was approved by the Rambam Institutional Review Board, which waived the requirement for informed consent. We screened all patients who underwent ≥1 cardiac catheterizations (with or without PCI) between January 2000 and December 2018. We excluded patients who had an estimated glomerular filtration rate (eGFR) of <15 mL/min per 1.73 m^2 of body surface area, based on the CKD Epidemiology Collaboration equation.[20]

The data that support the findings of this study are available from the corresponding author on reasonable request, although they will be subject to data privacy rules and requirements of the Institutional Review Board.

For the main analysis, patients were divided into 3 groups based on the number of contrast exposures as follows:1, 2 or 3, and ≥4 procedures.

Contrast Agents

All patients received nonionic, low-osmolar contrast agents. Iopromide (Ultravist), nonionic, iodinated, low-osmolar contrast agent was used until the end of 2006; and iohexol (Omnipaque), a low-osmolar, nonionic, iodinated contrast agent (350 mg of iodine per milliliter; 780 mOsm per kilogram of water [Omnipaque, Amersham Health]), was used from 2007.

Study End Point

Because CA-AKI is often transient, any clinically relevant renal injury must be associated with longer-term persistent decline in kidney function (ie, progression to CKD). Therefore, the primary end point of the present study was a persistent worsening of renal function, defined as an increase in serum creatinine concentration of at least 50% from baseline at least 90 days after the last procedure.[21] At this time point, recovery of creatinine levels is expected in patients who experienced reversible CA-AKI.[22,23] Figure 1 demonstrates the repeated and cumulative contrast exposures in a single patient who underwent 7 procedures. The primary end point is determined on the basis of the last creatinine measurement after the last procedure.

Postprocedural CA-AKI was defined as an increase in serum creatinine of either ≥25% or ≥0.5 mg/dL (44.2 μmol/L) from baseline at 48 hours to 72 hours after the procedure.[24,25] Postprocedural CA-AKI was not part of the study end point but was considered as a time-dependent risk factor for persistent worsening renal function.

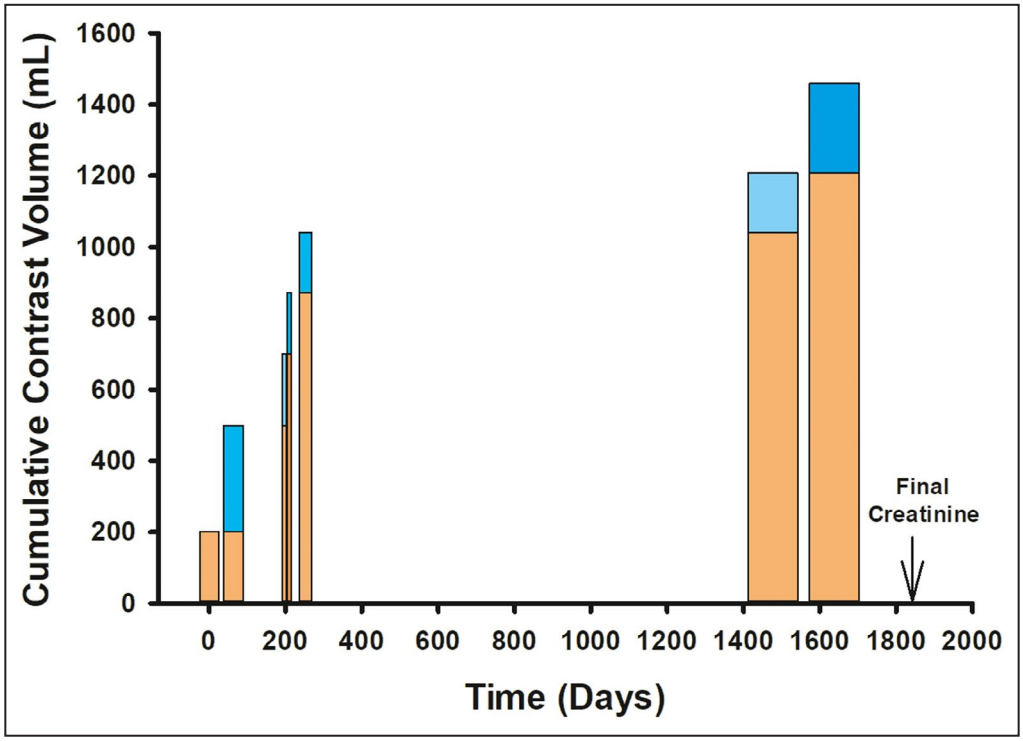

Figure 1. Repeated exposures to contrast media.
Cumulative contrast dose is shown for a single patient who underwent 7 contrast exposures over a period of 4.5 years. At each time point of contrast exposure, the bar shows the cumulative contrast dose up to this time point (orange) and at the current time point (magenta). Arrow indicates the last creatinine measurement.

Statistical Analysis

Data are expressed as mean±SD or median with interquartile range (IQR). The baseline characteristics and echocardiographic parameters of the study groups were compared using ANOVA for continuous variables and the χ^2 statistic for categorical variables. Continuous variables without a normal distribution are presented as median (IQR) and were compared using the Kruskal-Wallis test.

Univariable and multivariable time-dependent Cox regression analyses were performed to determine the relation between candidate variables and the primary end point of persistent worsening of renal function. Time-dependent Cox regression is the most appropriate method for analyzing cumulative and long-term drug exposure.[26] Patients were considered at risk for worsening renal function from the time of first CM exposure (the first procedure) through the last follow-up creatinine value. In the primary analysis, the relation of cumulative contrast dose and persistent worsening of renal function was assessed by means of Cox proportional hazards models, where the cumulative contrast exposure (dose) was allowed to increase with the time component of the regression model, with each repeated procedure as a time-dependent covariate.

The cumulative contrast dose was modeled as quartiles to avoid any arbitrary assumption about the functional form of the relationship with the outcome. The risk of persistent worsening renal function was modeled in the group in the higher quartiles of contrast dose versus the lowest quartile (reference hazard ratio [HR], 1.0).

Other potential risk variables considered in the multivariable procedure included age, sex, history of prior infarction, history of diabetes, history of hypertension, smoking, baseline estimated eGFR (modeled with a linear and a quadratic term to account for a nonlinear relationship with the outcome), presence of anemia, history of heart failure, coronary revascularization in the setting of acute coronary syndrome, and concomitant medical therapies (including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, and diuretics). Variables that changed during the follow-up (eg, new diabetes or acute coronary syndrome) were updated on the basis of new information at each procedure and used in the Cox model as time-dependent covariates.

Variables demonstrating an association with worsening renal function on univariate analysis at the $P<0.1$ level were used in a stepwise multiple Cox regression model with backwards elimination variable selection.

Additional analyses were performed using propensity score estimates, representing the probability of a patient to undergo >1 coronary intervention. Propensity scores were generated using a nonparsimonious multiple logistic regression model derived from baseline clinical and laboratory parameters. Following propensity score generation, patients were matched by using 1:1 nearest neighbor (Greedy-type) matching without replacement and a caliper width of a 0.2-SD of the propensity score logit. Matching was performed without replacement, and nonmatched results were discarded. The resulting matched pairs were similar in terms of their baseline clinical characteristics but different in the cumulative contrast exposure.

We assessed the success of the matches by examining standardized differences (measured in percentage points) in the observed confounders between the matched single and multiple CM exposures groups. Small (<10%) standardized differences support the assumption of balance between groups based on observed confounders.[27]

Following propensity score matching, methods that account for the matched nature of the sample were used. The marginal homogeneity (Stuart-Maxwell) test was used to compare categories of eGFR of the matched groups. Cox proportional hazards model with robust SEs (to account for dependence among matched subjects)[28] was used to assess the risk for persistent worsening of renal function.

Differences were considered statistically significant at the 2-sided $P<0.05$ level. Statistical analyses were performed using the Stata Version 16.1 (Stata, College Station, TX).

RESULTS

Baseline Characteristics

A total of 14 443 consecutive patients underwent ≥1 cardiac catheterizations (with or without PCI) between January 2000 and December 2018 (total of 20 672 procedures). Of these patients, 2942 met the study inclusion criteria (Figure 2). Each patient underwent between 1 and 9 procedures (total of 6135 procedures). The median time interval between procedures was 218 days (IQR, 47–603 days).

The baseline characteristics of the study participants, according to the number of repeated procedures, are summarized in Table 1. Baseline creatinine was similar

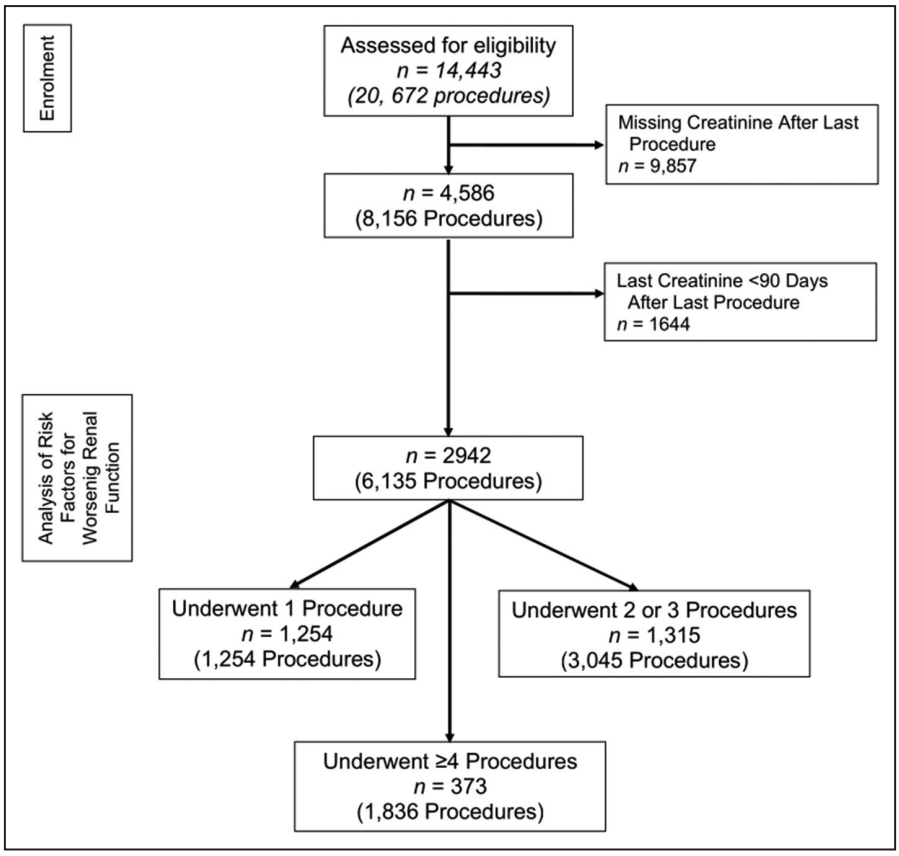

Figure 2. Consolidated Standards of Reporting Trials patient flow diagram.

among the 3 study groups, with slightly higher eGFR in patients undergoing a greater number of procedures. Patients who underwent a greater number of procedures were younger, were more likely to be men, and were more likely to have had a previous myocardial infarction and to be treated with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Patients with a greater number of procedures were less likely to be hypertensive or with anemia.

The median duration of follow-up from the first procedure to the final creatinine measurement was 32 months (IQR, 12–42 months). The final creatinine measurement was obtained after a median of 14 months (IQR, 3–34 months) from the last contrast exposure.

Figure 3A shows the cumulative contrast exposure by the number of procedures. The cumulative contrast dose followed a log-normal distribution (Figure 3B). The median cumulative contrast dose that was administered in patients who underwent a single procedure was 130 mL (IQR, 100–180 mL). The median cumulative contrast dose was 371 mL (IQR, 270–500 mL) in patients with 2 or 3 procedures and 762 mL (IQR, 602–961 mL) in patients undergoing ≥4 procedures.

Relationship Between Cumulative Contrast Dose and Persistent Worsening Renal Function

During the follow-up period, serum creatinine increase ≥50% above baseline ≥90 days after the last procedure occurred in 190 patients (6.5%), with 77 (6.1%), 90 (6.8%), and 23 (6.2%) of patients in the respective 3 study groups (P=0.75). In a univariable Cox regression model, several variables were associated with the primary end point, including age, baseline eGFR, diabetes, heart failure, anemia, acute coronary syndrome, CA-AKI occurring shortly after the procedure, and use of diuretics (Table 2). After multivariable adjustments, baseline eGFR, diabetes, heart failure, acute coronary syndrome, anemia, and CA-AKI remained independent predictors of persistent worsening renal function (Table 2). The cumulative CM dose was not associated with the primary end point of serum creatinine increase ≥50% above baseline ≥90 days after the last procedure in both the univariable and the multivariable models (P_{trend}=0.30 for quartiles of contrast dose; Table 2). There was no interaction between the cumulative contrast dose and baseline eGFR with regard to the primary end point (P=0.13).

Table 1. Baseline Characteristics

Variable	No. of procedures			
	1 (n=1254)	2–3 (n=1315)	4–9 (n=373)	*P* value
Age, y	61±11	61±11	57±11	<0.0001
Female sex	268 (21)	245 (19)	56 (15)	0.02
Serum creatinine (mg/dL)	1.0±0.3	1.0±0.2	1.0±0.3	0.69
μmol/L	88.4±26.5	88.4±17.7	88.4±26.5	
Baseline eGFR, mL/min per 1.73 m^2	81±21	82±19	85±20	0.002
Baseline eGFR <60 mL/min per 1.73 m^2	324 (19)	230 (17)	53 (14)	0.14
Baseline hemoglobin, g/dL	14.0±1.6	14.0±1.6	14.2±1.5	0.08
Baseline anemia*	219 (17)	209 (16)	45 (12)	0.04
Prior myocardial infarction	139 (11)	237 (18)	92 (25)	<0.0001
Diabetes	389 (31)	382 (29)	102 (27)	0.32
Hypertension	890 (71)	844 (64)	236 (63)	<0.0001
Acute coronary syndrome	614 (49)	740 (56)	223 (60)	<0.0001
Heart failure	327 (26)	301 (23)	88 (24)	0.16
Medical therapies				
ACE inhibitors/ARBs	241 (33)	339 (37)	112 (41)	0.046
Diuretics	89 (12)	122 (13)	28 (10)	0.45
Cumulative contrast dose, mL	130 (100–180)	371 (270–500)	762 (602–961)	<0.0001
Follow-up time to final creatinine measurement, mo	19 (2–39)	37 (23–54)	46 (31–68)	<0.0001

Data are given as mean±SD, number (percentage), or median (interquartile range). Continuous variables were compared using ANOVA or the Kruskal-Wallis test, and categorical variables were compared by the χ^2 statistic. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; and eGFR, estimated glomerular filtration rate.

*World Health Organization definition (hemoglobin levels <13 g/dL in men and <12 g/dL in women).

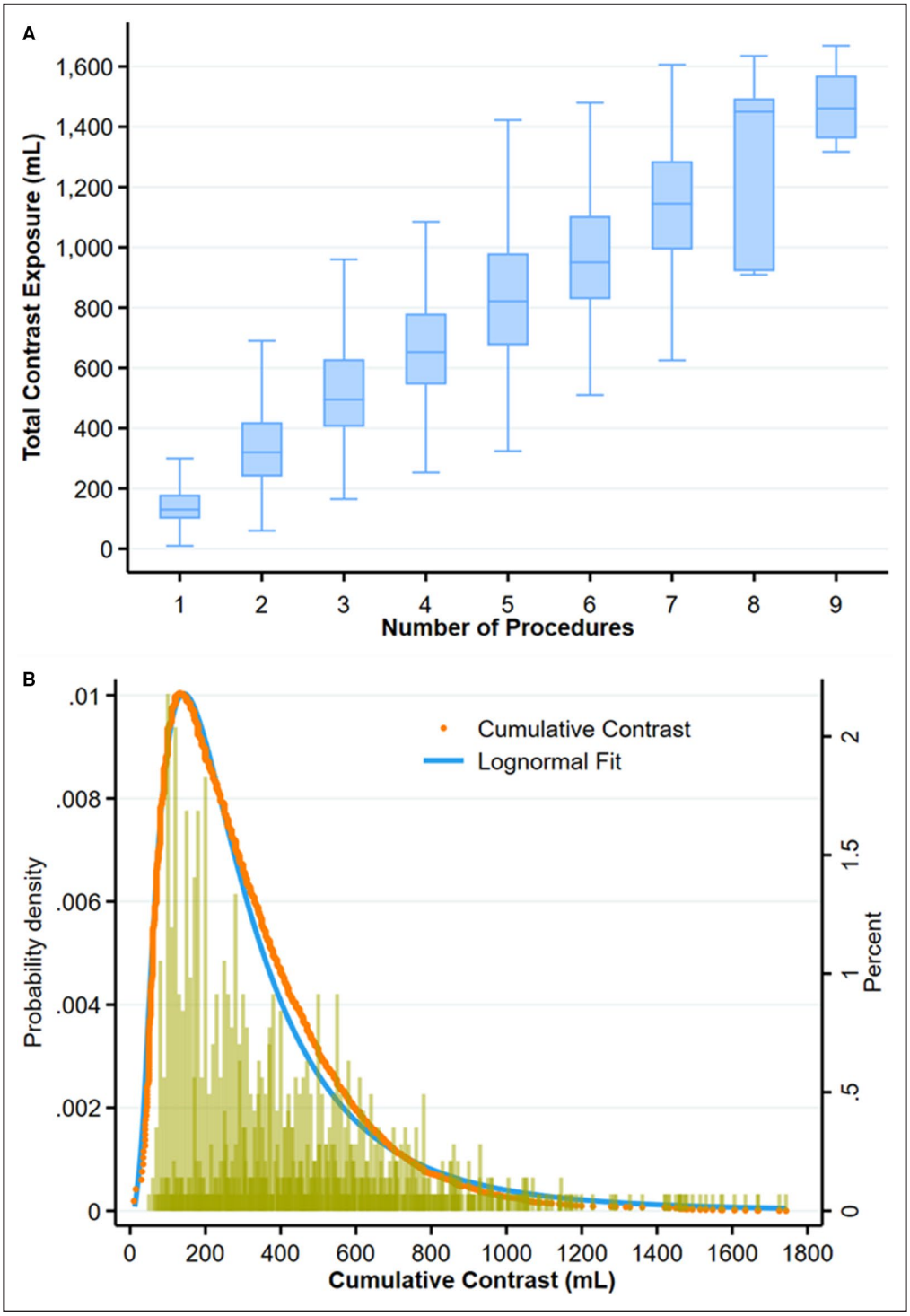

Figure 3. Cumulative contrast exposure and distribution.
A, Box-and-whisker plots of total contrast exposure by number of procedures. The line within the box denotes the median, and the box spans the interquartile range (25th–75th percentile). Whiskers extend from the 5th to 95th percentiles. **B**, Distribution of the cumulative contrast dose. Density probability plots (green circles) showing fit of cumulative contrast dose to log-normal distribution (orange line). Bars show the frequency distribution (expressed as percentage of the entire study population; right vertical axis).

Occurrence of CA-AKI

CA-AKI per procedure occurred in 6.1% (76 of 1254 procedures), 8.3% (252 of 3045 procedures), and 6.1% (112 of 1836 procedures) of patients who underwent a single procedure, 2 or 3 procedures, and ≥4 procedures, respectively.

Table 2. Unadjusted and Adjusted Cox Regression Model for Creatinine Increase >50% Above Baseline

Variable	Unadjusted			Adjusted		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Quartile of cumulative contrast dose						
First quartile (≤233 mL)	1.0	(Referent)		1.0	(Referent)	
Second quartile (234–419 mL)	0.91	0.61–1.36	0.65	1.00	0.67–1.51	0.99
Third quartile (420–669 mL)	0.82	0.55–1.22	0.32	0.88	0.59–1.31	0.53
Fourth quartile (≥509 mL)	1.18	0.81–1.72	0.38	1.29	0.89–1.88	0.22
Age (per 10-y increase)	1.47	1.28–1.68	<0.0001	…	…	…
Male sex	0.55	0.40–0.76	<0.0001	…	…	…
Baseline eGFR (per 10–mL/min per 1.73 m^2 decrease)	1.28	1.20–1.38	<0.0001	1.17	1.09–1.25	<0.0001
CA-AKI after the procedure	2.03	1.32–3.12	0.001	1.55	1.01–2.40	0.047
Diabetes	2.22	1.74–3.13	<0.0001	1.54	1.14–2.07	0.005
Acute coronary syndrome	1.99	1.47–2.69	<0.0001	1.93	1.43–2.61	<0.0001
Anemia	3.32	2.47–4.46	<0.0001	2.04	1.47–2.84	<0.0001
Use of diuretics	2.30	1.71–3.09	<0.0001	…	…	…
Heart failure	2.78	2.09–3.69	<0.0001	2.06	1.50–2.71	<0.0001

CA-AKI indicates contrast-associated acute kidney injury; eGFR, estimated glomerular filtration rate; and HR, hazard ratio.

Although CA-AKI was an independent predictor of the primary end point (Table 2), most patients with CA-AKI did not develop the primary end point. Of the 385 patients with at least one CA-AKI event after a procedure, only 46 (11.9%) developed persistent serum creatinine increase ≥50% above baseline. In addition, of the 190 patients who developed serum creatinine increase ≥50% above baseline at the end of follow-up, 144 (75.8%) did not develop CA-AKI at any time point. Figure 4 shows that CA-AKI did not affect the likelihood of subsequent procedures.

Propensity Score Matching

From the original cohort, 384 (30.6%) participants who underwent 1 procedure were matched on their propensity score to 384 (22.7%) patients who received ≥1 procedure (range, 2–9 procedures). After propensity score matching, the mean standardized difference in covariates between the 2 groups decreased from 9.7% (range, 0.6%–40.3%) before matching to 2.0% (range, 0.0%–4.3%) after matching (Figure 5).

After matching, patients were well balanced with respect to the individual variables included in the propensity model, with absolute standard differences between <10% for all variables (Figure 5). In the matched cohort, there were no significant differences between the groups for all clinical characteristics (Table 3), such that patients differed only in the number of procedures performed and, therefore, the total contrast exposure.

Following propensity score matching, serum creatinine increase ≥50% above baseline occurred in 28 patients (7.3%) in patients undergoing 1 procedure and 24 patients (6.3%) in patients undergoing 2 to 9 procedures (risk difference, 1.0%; 95% CI, −4.8% to 2.8%). Compared with the 1 procedure group, the HR for serum creatinine increase ≥50% above baseline was 0.76 (95% CI, 0.44–1.32; *P*=0.33) in the >1 procedure group, despite a large difference in the cumulative contrast exposure (Figure 6). When renal function was assessed on the basis of CKD stages, the matched groups were similar at the final creatinine measurement (Figure 7; marginal heterogeneity test *P*=0.54).

DISCUSSION

Patients undergoing PCI are exposed to a diverse and dynamic mixture of risk factors that can promote the loss of renal function. Although sequential exposure to CM is a common occurrence, risk assessments have focused solely on the narrow question of short-term harm from a single CM exposure.

The present study demonstrates that in patients with multiple exposures to CM, worsening of renal function over time is strongly associated with known risk factors for the progression of kidney disease, including baseline eGFR, diabetes mellitus, anemia, acute coronary events, and heart failure. However, despite large differences in the cumulative burden of CM exposure in the study patients, contrast volume was not associated with a persistent decline in kidney function. Furthermore, CA-AKI occurring shortly after CM administration accounts for a small proportion of the cases of long-term worsening renal function.

Contrast agents are believed to be directly toxic to tubular epithelial cells, leading to loss of function with apoptosis and necrosis.[25] CM, including low-osmolar

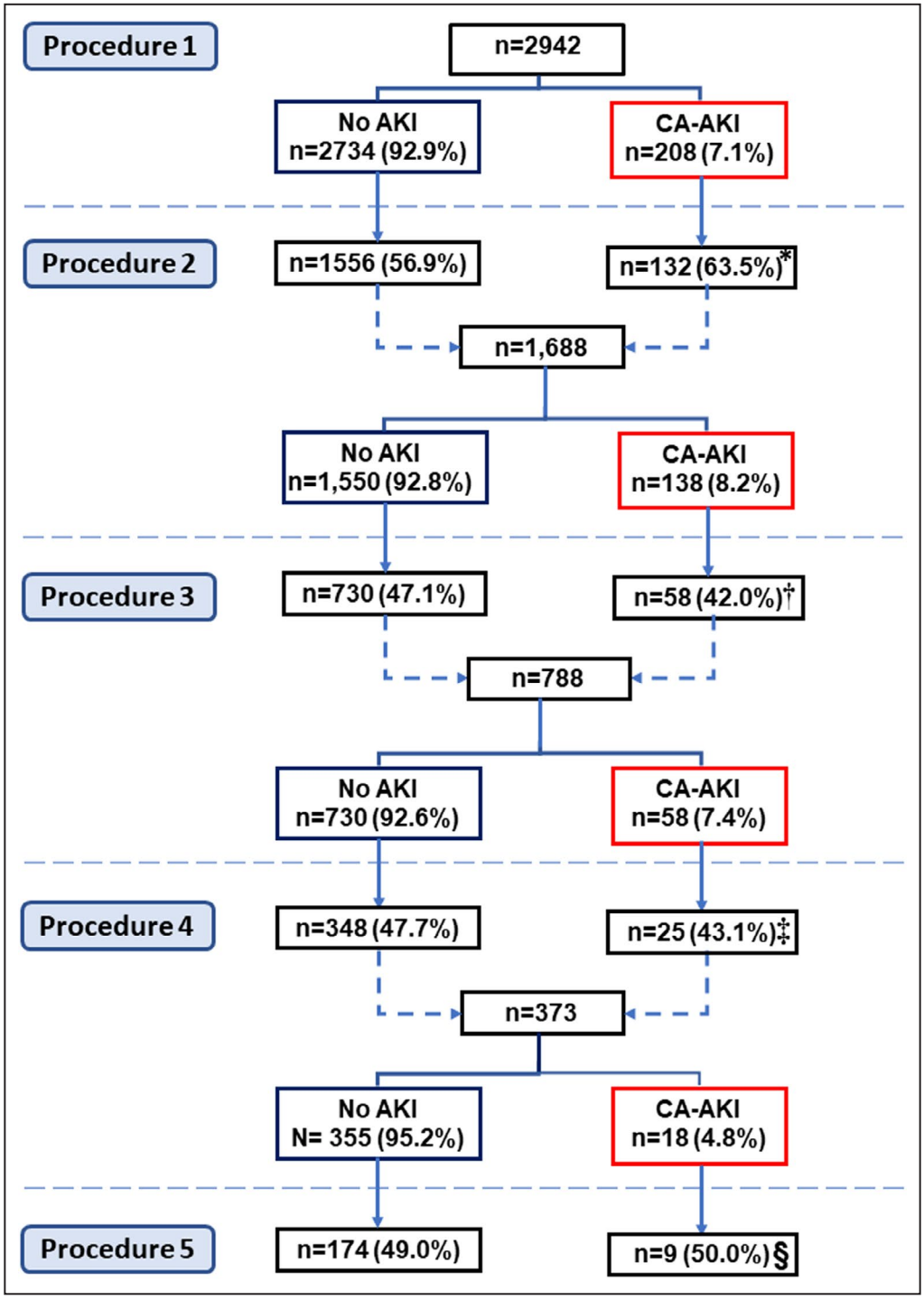

Figure 4. Relationship between contrast-associated acute kidney injury (CA-AKI) and the probability of subsequent procedures.
For each procedure (up to the fifth procedure), the figure shows the proportion of patients with CA-AKI and the proportion of patients undergoing a subsequent procedure (with and without CA-AKI). The probability of subsequent procedures was similar in patients with and without CA-AKI. *P=0.07, †P=0.25, ‡P=0.50, §P=0.94.

CM, affects diverse signaling pathways in human renal tubular cells that are involved in cell survival, death, and inflammation.[29]

For some renal toxins, the cumulative lifetime dose from either continuous or intermittent exposure determines the onset and severity of renal function

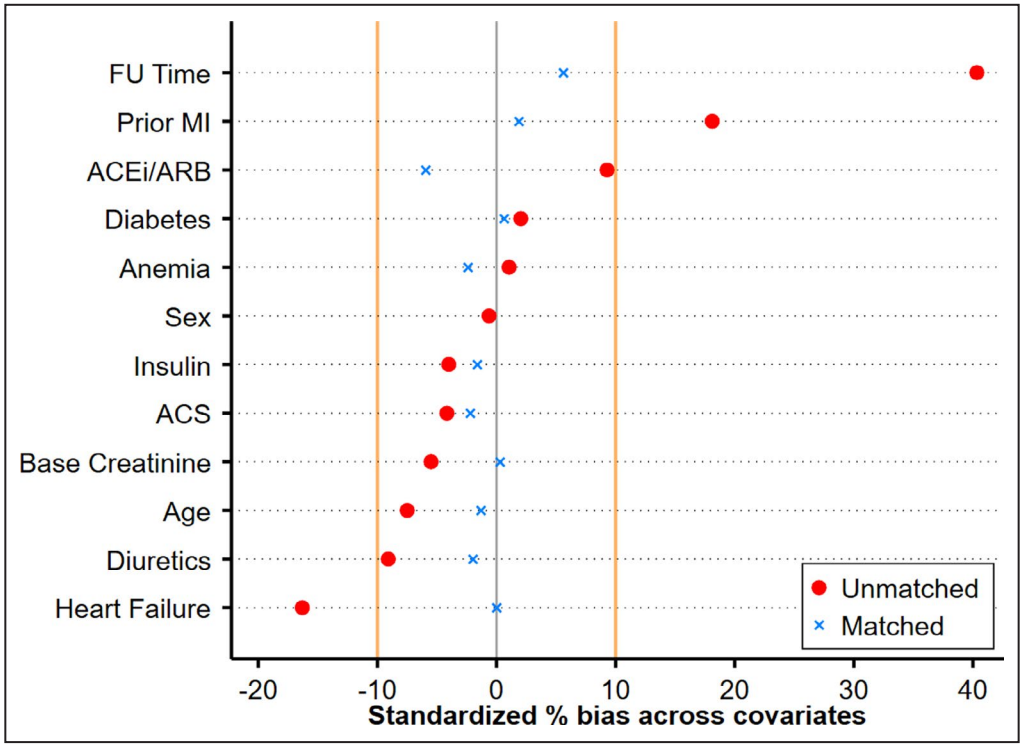

Figure 5. Covariable balance before (red circles) and after (green exes) matching.
The standardized differences after propensity matching (blue lines) are all well within 10%.

decline.[30–32] Furthermore, certain forms of chronic renal injury may be a consequence of repeated exposure to acute ischemic[33] or inflammatory[34] insults. Therefore, the long-term consequences of repeated episodes of CM exposure on kidney function may be an unrecognized medical burden. We hypothesized

Table 3. Baseline Clinical Characteristics in the Propensity-Matched Patients

Characteristics	1 Procedure (n=384)	2–9 Procedures (n=384)	*P* value
Age, y	61±11	61±12	0.81
Female sex	75 (20)	76 (20)	0.93
Serum creatinine			1.0
mg/dL	1.0±0.3	1.0±0.3	
μmol/L	88.4±26.5	88.4±26.5	
Baseline eGFR, mL/min per 1.73 m^2	79±19	79±17	0.78
Baseline hemoglobin, g/dL	14.2±1.5	14.2±1.5	0.81
Baseline anemia	45 (12)	42 (11)	0.75
Prior myocardial infarction	76 (20)	79 (21)	0.77
Hypertension	157 (41)	174 (45)	0.22
Diabetes	94 (24)	94 (24)	1.0
Acute coronary syndrome	258 (67)	454 (66)	0.77
Heart failure	83 (22)	83 (22)	1.0
Medical therapies			
ACE inhibitors/ARBs	133 (35)	122 (32)	0.40
Diuretics	27 (7)	25 (7)	0.77
Follow-up time to final creatinine measurement, y	3.21±1.34	3.28±1.39	0.27

Data are given as number (percentage) or mean±SD. For the matched group, comparisons were done with paired *t*-tests, Wilcoxon matched-pairs signed-rank test, or the McNemar test. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; and eGFR, estimated glomerular filtration rate.

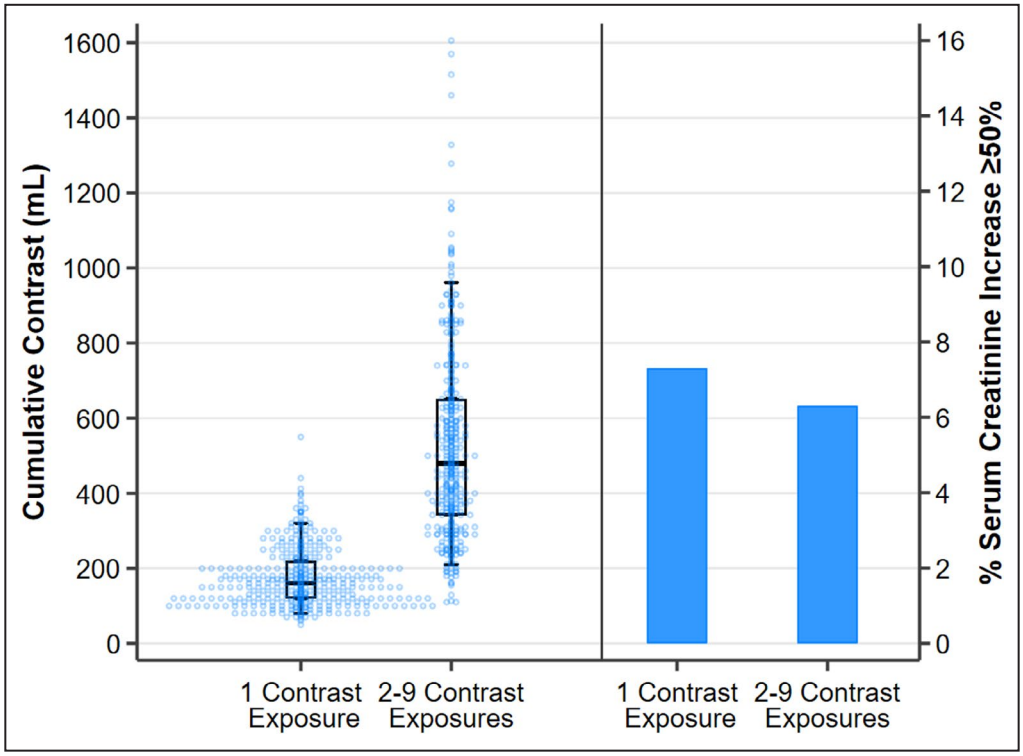

Figure 6. Total contrast exposure in the propensity-matched groups.
The line within the box denotes the median, and the box spans the interquartile range (25th–75th percentile). Whiskers extend from the 5th to 95th percentiles. Blue circles indicate individual measurements. Figure also shows the event rate for serum creatinine increase ≥50% above baseline.

that repeated CM exposures may produce subclinical renal dysfunction, culminating in a more rapid decline in renal function. Such subclinical renal damage may occur either as small creatinine elevations not classified as AKI during the immediate postprocedure period or as CA-AKI with partial recovery, ultimately leading to long-term loss of renal function. However, we were unable to substantiate this hypothesis. These finding are clinically relevant and reassuring with regard to the common scenario of repetitive CM exposure.

Several studies reported that patients with CA-AKI experienced larger decrements in eGFR over time.[35,36] These studies, however, ignore the possibility of interim additional CM exposures during follow-up and lack a control group.

Several recent studies found no association between contrast exposure and adverse renal outcomes, particularly with intravenous contrast-enhanced examinations.[6–9,11,12] The current results may also be germane to the present uncertainty about the causal association of CM and AKI in the setting of intra-arterial CM administration.

The traditional interpretation of biological gradient dictates that the presence of a dose-effect relationship (ie, increased exposure resulting in increased incidence of disease) supports the causal association between an exposure and effect.[37] The lack of any such dose-effect relationship in the current study is an important consideration against a potential causal relationship.

Epidemiologic and mechanistic studies suggest that AKI and CKD are closely interconnected,[38] with AKI being a risk factor for the development of CKD. A substantial proportion of patients with true AKI, even those with normal baseline renal function, recover only partially with residual structural damage,[39] and are at risk for progression to advanced stages of CKD.[40–42]

In the present study, CA-AKI occurring shortly after CM exposure was independently associated with long-term worsening renal function. These results support the concept of AKI leading to future CKD in the context of repeated cardiac interventions. However, only ≈11% of CA-AKI events were associated with persistent worsening of renal function.

Study Limitations

It is important to consider several limitations pertinent to the methods of this study. First, this was a single-center post hoc analysis of our cardiac catheterization laboratory data, and thus, the results must be regarded as hypothesis generating and exploratory and require validation in other studies. More than half of the patients assessed for eligibility were excluded because of

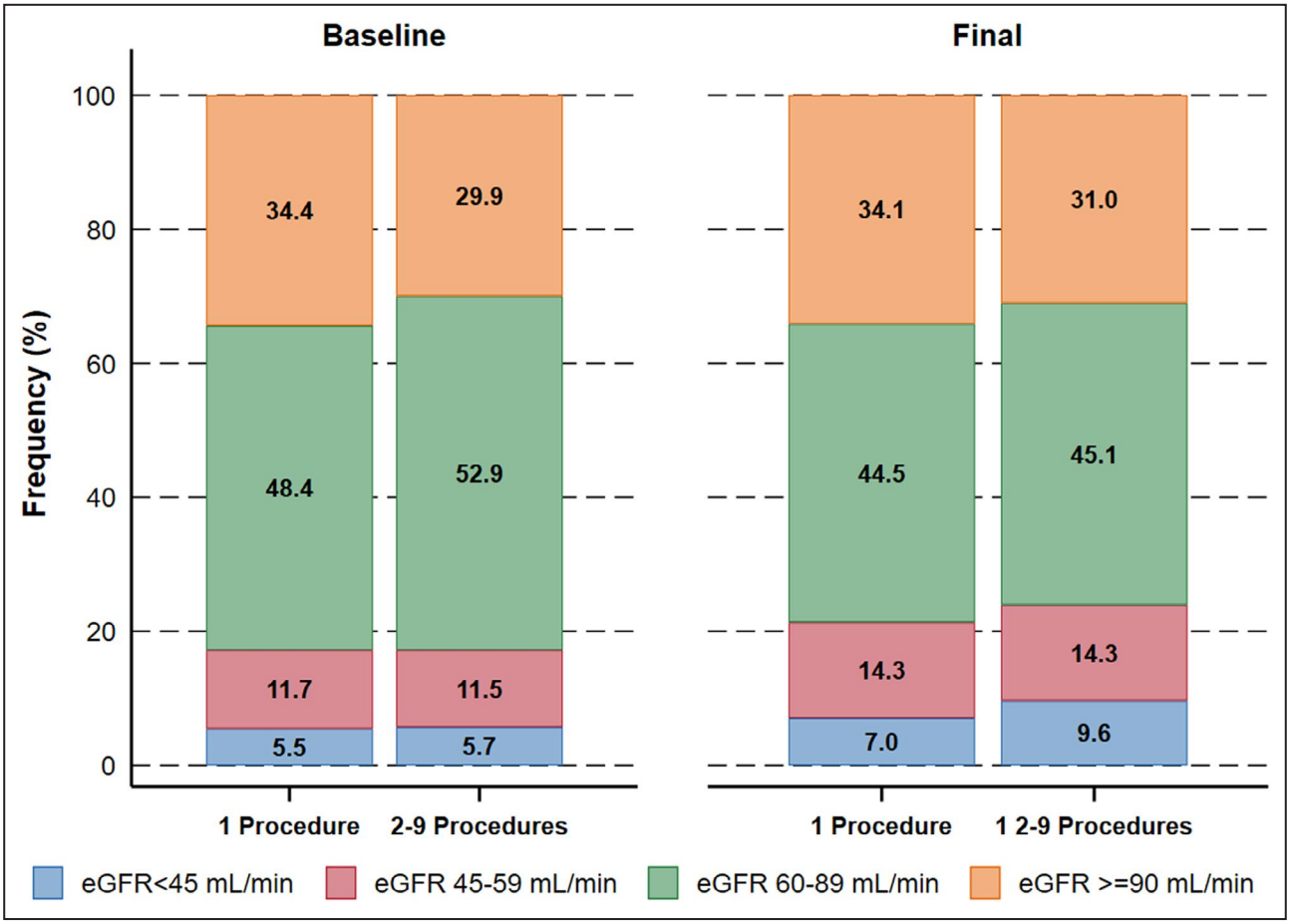

Figure 7. Categories of estimated glomerular filtration rate at baseline and final creatinine measurement in the propensity-matched groups (marginal heterogeneity test *P*=0.54 for the comparison of glomerular filtration rate categories at the final assessment).

missing creatinine measurements, which may impact the generalizability of the study. The study population included predominantly patients with preserved renal function at baseline, and contrast exposures generally occurred at long intervals. Unrecorded events that affect renal function may have occurred during the long-term follow-up. Sampling bias may have occurred because patients at higher risk for CA-AKI were less likely to be referred to repeated procedures (ie, the multiprocedure group is enriched in healthier patients who are less likely to develop renal dysfunction).

CONCLUSIONS

In patients with multiple exposures to CM, worsening of renal function over time is strongly associated with known risk factors for the progression of kidney disease but not with the cumulative contrast volume. The lack of dose-effect relationship in the studied population does not support the causal association between CM exposure and renal dysfunction.

ARTICLE INFORMATION

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None.

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