Acute Kidney Injury After Primary Angioplasty: Is Contrast-Induced Nephropathy the Culprit?

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Background—Acute kidney injury (AKI) following primary percutaneous coronary intervention (pPCI) is frequently interpreted as contrast-induced AKI but may result from other insults. We aimed to determine the causal association of contrast material exposure and the incidence of AKI following pPCI using a control group of propensity score–matched patients with ST-segment–elevation myocardial infarction who were not exposed to contrast material.

Methods and Results—We studied 2025 patients with ST-segment–elevation myocardial infarction who underwent pPCI and 1025 patients receiving fibrinolysis or no reperfusion who were not exposed to contrast material during the first 72 hours of hospital stay (control group). AKI was defined as creatinine of ≥0.5 mg/dL or >25% rise within 72 hours. AKI rates were similar in the pPCI and control groups (10.3% versus 12.1%, respectively; $P=0.38$). Propensity score matching resulted in 931 matched pairs with PCI and no PCI, with balanced baseline covariates (standardized difference <0.1). Among propensity score–matched patients, AKI rates were not significantly different with and without PCI (8.6% versus 10.9%, $P=0.12$). In the pPCI cohort, independent predictors of AKI included age ≥70 years, insulin-treated diabetes mellitus, diuretic therapy, anterior infarction, baseline estimated glomerular filtration rate, and variables related to the presence of pump failure (higher Killip class, intra-aortic balloon pump use) and reduced left ventricular ejection fraction but not contrast material dose. A risk score based on the PCI cohort had similar discriminatory capacity for AKI in the control group (C statistic 0.81±0.02 and 0.78±0.02, respectively; $P=0.26$).

Conclusions—The development of AKI in patients with ST-segment–elevation myocardial infarction undergoing pPCI is mainly related to older age, baseline estimated glomerular filtration rate, heart failure, and hemodynamic instability. Risk for AKI is similar among ST-segment–elevation myocardial infarction patients with and without contrast material exposure. (***J Am Heart Assoc.*** 2017;6:e005715. DOI: 10.1161/JAHA.117.005715.)

Patients undergoing primary percutaneous coronary intervention (pPCI) are considered to be at higher risk of contrast medium (CM)–induced acute kidney injury (CI-AKI) compared with those undergoing elective interventions.[1] Several studies have shown that CI-AKI following pPCI is associated with increased mortality.[2,3] In these studies, AKI is frequently interpreted as CI-AKI.[1,3] However, CI-AKI is defined as an acute deterioration of renal function after administration of radiocontrast media in the absence of other alternative explanations for renal impairment.[4,5] Although this may be a reasonable assumption in patients undergoing elective PCI, deterioration of renal function after pPCI may be the result of multiple other contributing factors including hemodynamic alterations, neurohormonal activation, and initiation of nephrotoxic drugs.

Recent studies evaluating the propensity of contrast exposure to induce AKI in noncardiovascular settings demonstrated that intravenous contrast is not an independent risk factor for AKI, dialysis, or mortality.[6–8] Importantly, because studies linking CM use to AKI in the setting of pPCI lack a control group in which CM was not administered, it is impossible to distinguish CM-dependent AKI from multiple additional risk factors other than exposure to contrast media.[9] Consequently, studies that include ST-segment–elevation myocardial infarction (STEMI) patients who were not exposed to CM are desirable.

The aim of the present study was to identify the specific clinical correlates that produced AKI in patients with acute ST-elevation myocardial infarction undergoing pPCI, and the relative contribution of contrast media exposure to the development of AKI. We also sought to compare the incidence of AKI between STEMI patients with and without CM exposure.

Methods

We used a prospective database consisting of all STEMI patients admitted to the intensive care unit at the Rambam Medical Center, Haifa, Israel, from January 2000 and September 2015. The investigational review committee on human research approved the study protocol, and the need for written informed consent was specifically waived.

The decision to use pPCI was based on the practice at the time the patient was admitted. In the beginning of the period, patients eligible for reperfusion (generally those admitted within 12 hours from symptom onset) were treated mainly with thrombolytic therapy, although patients perceived to be at high risk (eg, those with hemodynamic instability, large anterior infarction) were submitted to pPCI. Over the years,

the proportion of primary PCI as the preferred treatment modality in STEMI increased, and from mid-2007, all patients underwent pPCI.

Primary PCI Cohort

The cohort included consecutive STEMI patients who underwent pPCI. All patients received nonionic, low-osmolar, iodinated contrast agents.

Thrombolysis/No Reperfusion Cohort

This cohort included patients who were admitted during the same period, who were treated with thrombolysis or who received no reperfusion therapy at all, and who were not exposed to CM during the first 72 hours of hospital stay. This cohort served to study the risk of developing AKI in the absence of contrast exposure in the setting of STEMI.

Assessment of Renal Function

Venous blood samples were obtained at admission and at 24, 48, and 72 hours thereafter. After the first 72 hours from admission, creatinine measurements were checked only when clinically indicated. Estimated glomerular filtration rate (eGFR) was calculated based on the abbreviated MDRD (Modification of Diet in Renal Disease) study equation.

Definitions

AKI was defined as an increase in serum creatinine concentration ≥ 0.5 mg/dL compared with admission value or a >25% relative rise during the first 72 hours after the procedure.[3]

Several predictive indices for AKI after radiocontrast administration were calculated for each patient:

1. Maximum contrast dose using an empirical formula: maximum contrast dose (mL)=(5×body weight [kg])/ serum creatinine (mg/dL).[10] The contrast ratio is determined by dividing the administered contrast amount by the calculated maximum contrast dose.
2. Total volume of contrast given divided by creatinine clearance (shown as CrCl), as estimated by the Cockcroft-Gault method: V/CrCl.
3. The total volume of contrast given divided by eGFR: V/ eGFR.[11]

Statistical Analysis

The baseline characteristics of groups were compared using the unpaired *t* test for continuous variables and the χ^2

statistic for noncontinuous variables. The area under the receiver operating characteristic (ROC) curve was used as a measure that reflects the discriminatory power of each predictive index for the diagnosis of AKI. Areas under the ROC curves were compared using the DeLong method.

The amount of contrast agent was modeled using an indicator variable (quartiles of the distribution). Logistic regression was performed with AKI as the dependent variable to model the association between contrast volume and other potential risk factors and the development of AKI. Stepwise variable selection with a significance level of 0.05 (Wald test) for variable retention was used to develop parsimonious predictor models. All variables in Table 1 were considered for the model. Model discrimination was assessed by the area under the ROC curve.

Table 1. Baseline Clinical Characteristics of the pPCI Cohort

Characteristics	No AKI (n=1816)	AKI (n=209)	P Value
Age, y	59±12	66±13	<0.0001
Female sex	324 (18)	51 (24)	0.02
Weight, kg	81±16	79±17	0.16
Hypertension	806 (44)	122 (61)	<0.0001
Diabetes mellitus			
Noninsulin treated	380 (21)	46 (22)	0.72
Insulin treated	66 (4)	26 (12)	<0.0001
Killip Class II–III	185 (10)	53 (25)	<0.0001
Killip Class IV or IABP use	82 (6)	57 (27)	<0.0001
Previous infarction	384 (19)	50 (24)	0.10
Anterior infarction	858 (47)	134 (64)	<0.0001
Left ventricular ejection fraction <45%	556 (31)	124 (59)	<0.0001
Baseline renal function			
Baseline creatinine, mg/dL	0.99±0.32	1.32±0.87	<0.0001
Baseline eGFR, mL/min per 1.73 m²	82±22	65±30	<0.0001
eGFR <60 mL/min per 1.73 m²	850 (47)	143 (68)	<0.0001
Baseline hemoglobin	14.0±1.6	13.5±2.0	0.0001
Medical therapy			
Antiplatelet agents	1811 (100)	209 (100)	0.45
Beta blockers	764 (89)	84 (81)	0.01
ACE inhibitors/ARBs	766 (89)	85 (82)	0.02
Diuretics	240 (28)	49 (47)	<0.0001

Data are number (%) or mean±SD. ACE indicates angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin-receptor blocker; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; pPCI, primary percutaneous coronary intervention.

An additive risk score for the prediction of AKI was developed on the pPCI cohort from the multiple logistic regression model by using a regression coefficient–based scoring method.[12] For simplicity of use, scores were approximated by rounding coefficients to the nearest half integer. The risk score was used to predict AKI in the cohort of patients who were not exposed to CM.

To investigate the effect of contrast exposure on the change in creatinine levels in the first 72 hours as a continuous variable, we adopted a linear mixed-model approach with random slopes and intercepts. The model included terms for pPCI versus no pPCI, baseline creatinine, time, and an interaction term between pPCI and time. This model also included other covariates that potentially affected the change in creatinine as fixed effects.

Propensity score estimates representing the probability of pPCI were generated in both the CM (pPCI) and non-CM groups by using a logistic regression model derived from 16 clinical variables (Table 1). Following propensity score generation, patients were matched by using 1:1 nearest neighbor (greedy type) matching and a caliper width of 0.1 standard deviation of the propensity score logit. Matching was performed without replacement, and nonmatched results were discarded.

We assessed the success of the matches by examining standardized differences (measured in percentage points) in the observed confounders between the matched pPCI and non-pPCI groups.[13] Small (<10%) standardized differences support the assumption of balance between treatment groups based on observed confounders. The incidence of AKI was compared between CM and non-CM groups following propensity score matching by using the Fisher exact test.

Event-free survival curves were estimated by the Kaplan–Meier method and compared with the log-rank test. Univariate and multivariate Cox proportional hazards models were used to model the relationship between contrast volume and 1-year composite major adverse cardiac events (consisting of death, readmission for heart failure, and reinfarction). The model adjusted for all variables in Table 1. Variables found to show marginal association with mortality in univariate analysis (P<0.20) were used in the multivariate model.

Differences were considered statistically significant at the 2-sided P<0.05 level. Statistical analyses were performed using the Stata statistical software (version 13.1).

Results

Between January 2000 and December 2015, a total of 2200 patients presenting with acute STEMI underwent pPCI. Patients were excluded because of missing creatinine measurements (no repeated creatinine measurement; n=54) or contrast volume data (n=121). The remaining 2025 patients

composed the pPCI cohort. The thrombolysis/no reperfusion cohort included 1025 STEMI patients admitted during the same period, with 403 treated with thrombolytic agents and 622 who did not receive any reperfusion therapy.

Characteristics of the pPCI cohort according to AKI status are shown in Table 1. Patients who developed AKI during their hospital course were older and had a higher prevalence of hypertension and lower eGFR; they presented with higher Killip class and were more likely to have anterior infarction, present with cardiogenic shock, and to receive treatment with an intra-aortic balloon pump. Patients with AKI were less likely to receive β-blockers or angiotensin-converting enzyme inhibitors and more likely to receive diuretics.

Relationship of Contrast Volume and AKI

The median amount of contrast administered was 150 mL (interquartile range 100–200 mL; range 35–550 mL). Of the total 3050 patients, 22 (0.7%), 265 (8.7%), and 771 (25.3%) were missing creatinine values at the 24, 48, and 72 hours, respectively. Using the cutoff of ≥0.5 mg/dL or a 25% increase in serum creatinine, 209 of the 2025 pPCI patients (10.3%) developed AKI. The median contrast dose was 160 mL in patients with AKI (interquartile range 120–210 mL) and 150 mL (interquartile range 120–200 mL) in patients without AKI (P=0.12).

ROC analysis demonstrated that contrast volume alone was not a predictor of AKI (Figure 1). The calculation of V/

Figure 1. Comparison of areas under the receiver operator characteristic curves that relate various contrast media indices to the development of acute kidney injury. CrCl indicates creatinine clearance; eGFR, estimated glomerular filtration rate; Vol, volume.

eGFR displayed the best discriminatory power for AKI but with low accuracy overall (Figure 1).

The association of clinical variables and quartiles of V/eGFR with the risk of developing AKI was assessed using a logistic regression model. Significant univariable predictors of AKI included age, insulin-treated diabetes mellitus, lower hemoglobin levels, anterior infarction, Killip class and intra-aortic balloon pump (IABP) use, diuretic therapy, eGFR, and V/eGFR (Table 2, model 1).

After adjustments for eGFR alone, V/eGFR was no longer a significant predictor of AKI (P=0.47). In the final multivariable model, independent predictors of AKI included age ≥70 years, insulin-treated diabetes mellitus, diuretic therapy, anterior infarction, baseline eGFR, and variables related to the presence of pump failure (higher Killip class and use of IABP) and reduced left ventricular ejection fraction (Table 2, model 1).

Several sensitivity analyses were conducted for the logistic regression models with varying CM cutoffs and definitions of AKI. When contrast exposure was modeled in the whole study population, the adjusted odds ratio for AKI in patients undergoing primary PCI versus no PCI was 0.79 (95% confidence interval [CI], 0.60–1.05, P=0.10; Table 2, model 2).

We analyzed the effect of CM as a dichotomous variable above and below median value. Compared with patients with contrast volume below median value, the adjusted odds ratio for AKI was 1.15 (95% CI 0.83–1.59, P=0.39) in patients with contrast volume above median. When AKI was defined using a higher increments of serum creatinine (≥1.0 mg/dL or a ≥50% increase), the adjusted odds ratio for AKI in the upper quartile compared with the lower quartile of contrast volume was 1.18 (95% CI, 0.71–1.96; P=0.52).

We also tested the interaction between the effect of CM exposure and risk factors for AKI. There was no significant interaction between the effect of CM and eGFR <60 mL/min per 1.73 m^2 (P=0.39), diabetes mellitus (P=0.18), use of diuretics (P=0.07), age (P=0.12), Killip class (P=0.20), or reduced left ventricular ejection fraction (P=0.14).

Predictors of AKI in STEMI Patients Without pPCI

Table 3 shows the clinical characteristics of STEMI patients who underwent pPCI compared with those who did not undergo pPCI. Patients who were not treated with pPCI had more risk factors for AKI, including older age, worse baseline renal function, and higher rates of Killip class II or III. However, they were less likely to have cardiogenic shock, IABP use, or anterior infarction. Baseline renal function was slightly better in the pPCI cohort, and the use of β-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers was more frequent.
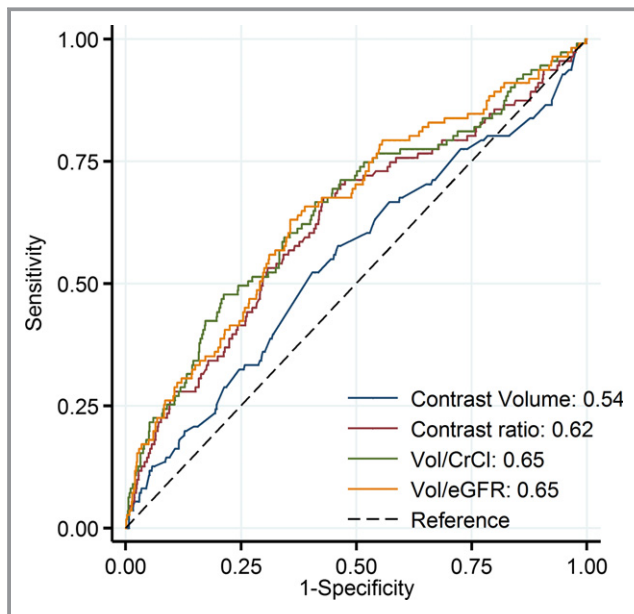
Table 2. Univariable and Multivariate Logistic Regression Model for AKI

Variable	Unadjusted		Multivariate Results	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Model 1: primary PCI patients				
Age ≥70 y	3.33 (2.47–4.88)	<0.0001	1.89 (1.33–2.71)	<0.0001
Hypertension	1.94 (1.45–2.60)	<0.0001	…	…
Diabetes mellitus				
No diabetes mellitus	1.0 (Referent)	…	1.0 (Referent)	…
Noninsulin treated	1.37 (0.98–1.91)	0.07	0.90 (0.61–1.32)	0.59
Insulin treated	3.34 (1.93–5.77)	<0.0001	2.03 (1.06–3.89)	0.03
Anterior infarction	2.00 (1.48–2.69)	<0.0001	1.51 (1.06–2.13)	0.02
eGFR, mL/min per 1.73 m^2				
≥60	1.0 (Referent)	…	1.0 (Referent)	…
30–59	3.41 (2.23–5.20)	<0.0001	1.71 (1.17–2.50)	0.005
<30	15.8 (6.19–40.30)	<0.0001	6.27 (3.15–12.49)	<0.0001
Hemoglobin (per 1-g/L increase)	0.81 (0.74–0.88)	<0.0001	…	…
Killip class I	1.0 (Referent)	…	1.0 (Referent)	
Killip class II–III	4.47 (3.10–6.47)	<0.0001	2.19 (1.45–3.31)	<0.0001
Killip class IV or IABP use	10.85 (7.31–16.09)	<0.0001	6.59 (4.30–10.08)	<0.0001
LVEF <45%	3.31 (2.27–4.43)	<0.0001	1.68 (1.18–2.39)	0.004
Diuretic therapy	4.02 (2.96–5.40)	<0.0001	1.81 (1.27–2.57)	0.001
V/eGFR quartile				
First (<2.0)	1.0 (Referent)	…	…	…
Second (2.0–2.8)	0.940 (0.54–1.51)	0.79	…	…
Third (2.9–3.8)	1.53 (0.97–2.43)	0.07	…	…
Fourth (>3.8)	3.40 (1.24–5.16)	<0.0001	…	…
Model 2: all patients				
Age ≥70 y	3.57 (2.83–4.51)	<0.0001	1.96 (1.48–2.60)	<0.0001
Hypertension	2.00 (1.58–2.52)	<0.0001	1.38 (1.05–1.80)	0.02
Diabetes mellitus				
No diabetes mellitus	1.0 (Referent)	…	1.0 (Referent)	…
Noninsulin treated	1.25 (0.96–1.64)	0.10	0.83 (0.62–1.13)	0.24
Insulin treated	3.60 (2.36–5.47)	<0.0001	2.08 (1.38–3.37)	0.003
Anterior infarction	1.91 (1.52–2.41)	<0.0001	1.53 (1.21–2.00)	0.002
eGFR, mL/min per 1.73 m^2				
≥60	1.0 (Referent)	…	1.0 (Referent)	…
30–59	3.65 (2.84–4.68)	<0.0001	1.71 (1.27–2.30)	<0.0001
<30	7.97 (5.03–12.63)	<0.0001	3.01 (1.75–5.17)	<0.0001
Hemoglobin (per 1-g/L increase)	0.85 (0.80–0.91)	<0.0001	0.98 (0.91–1.05)	0.56
Killip class I	1.0 (Referent)	…	1.0 (Referent)	…
Killip class II–III	4.73 (3.32–5.77)	<0.0001	1.99 (1.45–2.73)	<0.0001
Killip class IV or IABP use	12.18 (8.63–17.19)	<0.0001	7.43 (5.10–10.84)	<0.0001
LVEF <45%	2.88 (2.28–3.63)	<0.0001	1.44 (1.09–1.90)	0.011
Diuretic therapy	3.59 (2.85–4.54)	<0.0001	1.75 (1.32–2.32)	<0.0001
Primary PCI vs no PCI	0.84 (0.66–1.06)	0.14	0.79 (0.60–1.05)	0.10

ACE indicates angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

AKI occurred in 124 (12.1%) patients receiving either thrombolytic therapy or no reperfusion (*P*=0.14 compared with the pPCI cohort). The multivariable logistic model in Table 2 was used to generate a risk score for AKI based on the multivariate-adjusted coefficients as follows: age ≥70 years, 7 points; anterior infarction, 4 points, eGFR 30 to 60 mL/min per 1.73 m^2, 5 points; eGFR <30 mL/min per 1.73 m^2, 18 points; insulin therapy, 7 points; Killip class II or III, 8 points; Killip class IV or IABP use, 19 points; left ventricular ejection fraction <45%, 5 points; diuretic therapy, 6 points. Application of the risk score that was derived from the pPCI patients to the thrombolysis/no reperfusion population revealed a similar discriminatory capacity for AKI. The area under the ROC curve was 0.81±0.02 in the derivation pPCI group and 0.78±0.02 in thrombolysis/no reperfusion patients (*P*=0.26; Figure 2).

Propensity Score Matching

One-to-one matching of the propensity score yielded a total of 931 patient pairs. Patients were well matched with respect to the 16 variables included in the propensity model (Figure 3 and Table 3, right panel), with a mean difference in paired propensity scores of 0.8% (95% CI, −2.1% to 0.5%). Following propensity score matching, the incidence of AKI in both the CM group (80 AKI events, 8.6%) and the non−CM group (101 AKI events, 10.9%) was similar (odds ratio: 0.77; 95% CI, 0.56−1.06; *P*=0.12).

Table 3. Baseline Clinical Characteristics in Patients With and Without pPCI

Characteristics	Before Propensity Score Matching			After Propensity Score Matching		
	pPCI (n=2025)	Thrombolysis/No Reperfusion (n=1025)	*P* Value	pPCI (n=931)	Thrombolysis/No Reperfusion (n=931)	*P* Value
Age, y	60±13	63±13	<0.0001	62±12	62±13	0.33
Female sex	375 (19)	263 (26)	<0.0001	222 (24)	222 (24)	1.0
Hypertension	993 (46)	481 (47)	0.66	434 (47)	427 (46)	0.75
Diabetes mellitus						
Noninsulin treated	426 (21)	275 (27)	<0.0001	229 (25)	239 (26)	0.59
Insulin treated	92 (5)	30 (3)	0.03	25 (3)	28 (3)	0.68
Killip class II–III	238 (12)	195 (19)	<0.0001	144 (15)	151 (16)	0.66
Killip class IV or IABP use	139 (7)	28 (3)	<0.0001	23 (2)	27 (3)	0.57
Previous infarction	398 (20)	232 (23)	0.06	209 (22)	209 (22)	1.00
Anterior infarction	992 (49)	328 (32)	<0.0001	312 (34)	306 (33)	0.77
LVEF <45%	680 (34)	351 (34%)	0.71	305 (33)	328 (35)	0.26
Baseline renal function						
Baseline creatinine, mg/dL	1.03±0.42	1.06±0.37	0.03	1.04±0.35	1.04±0.46	0.67
Baseline eGFR, mL/min per 1.73 m^2	80±23	74±24	<0.0001	77±22	77±23	0.78
eGFR categories, mL/min per 1.73 m^2						
>60	1633 (80)	738 (62)	<0.0001	719 (77)	698 (75)	0.25
45–60	226 (11)	154 (15)	0.002	123 (13)	135 (15)	0.42
30–44	118 (6)	95 (9)	<0.0001	59 (6)	72 (8)	0.24
<30	48 (2)	38 (4)	0.04	30 (3)	26 (3)	0.59
Baseline hemoglobin	14.0±1.2	13.3±2.0	<0.0001	13.9±1.7	14.0±1.7	0.20
Medical therapy in hospital						
Antiplatelet agents	2020 (100)	986 (96)	<0.0001	928 (100)	925 (99)	0.32
Beta blockers	1811 (89)	841 (82)	<0.0001	801 (86)	786 (84)	0.33
ACE inhibitors/ARBs	1825 (90)	828 (81)	<0.0001	791 (85)	778 (84)	0.41
Diuretics	637 (31)	234 (23)	<0.0001	246 (26)	258 (28)	0.53

Data are number (%) or mean±SD. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; pPCI, primary percutaneous coronary intervention.

Assessment of Creatinine Changes as a Continuous Variable

We also modeled the change in renal function over the first 72 hours of hospital stay as a continuous variable in patients with and without CM exposure, using linear mixed models. Serum creatinine trajectory was linear over the first 72 hours of hospitalization, with a modest increase in both the pPCI and non-PCI groups of 0.036 mg/dL per day (95% CI, 0.023–0.050) and 0.037 mg/dL per day (95% CI, 0.027–0.047), respectively. There was no significant interaction between PCI and time with regard to creatinine change ($P=0.97$), indicating that the rate of change in serum creatinine was similar with and without PCI (Figure 4). Similar results were obtained after propensity score matching ($P=0.77$).

CM Exposure and Clinical Outcomes

Patients were followed for 1 year after study entry. During follow-up, the primary composite end point occurred in 589 patients (19.3%). Patients treated with pPCI and those who did not develop AKI had better clinical outcomes (Figure 5). In the group of patients who were treated with pPCI, the rates of the primary composite end point were 12.5% among those without AKI and 42.1% among those with AKI. Among patients not treated with pPCI, the respective rates of events were 22.1% versus 62.1%. These differences are presented graphically in Figure 5 in terms of the cumulative incidence of the primary end point in the 4 groups. Within the pPCI group,
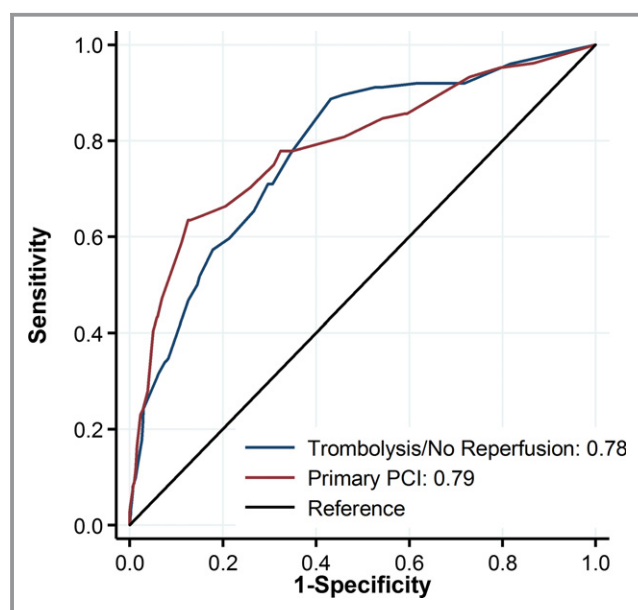
there was no significant variation in the 1-year event rate across quartiles of contrast volume (log rank, $P=0.81$).

In a multivariable Cox model, the adjusted hazard ratio [HR] for the primary end point was significantly increased with AKI among participants with pPCI (adjusted HR: 2.09; 95% CI, 1.59–2.75; $P<0.0001$) and without pPCI (HR: 2.01; 95% CI, 1.45–2.79; $P<0.0001$). There was no interaction between pPCI and AKI with regard to the primary end point; the interaction HR (ie, the ratio of the HRs for risk of AKI in the pPCI and no-pPCI groups) was 1.03 (95% CI, 0.68–1.58; $P=0.86$ for interaction), indicating that the hazard associated with AKI was similar in patients with and without contrast exposure.
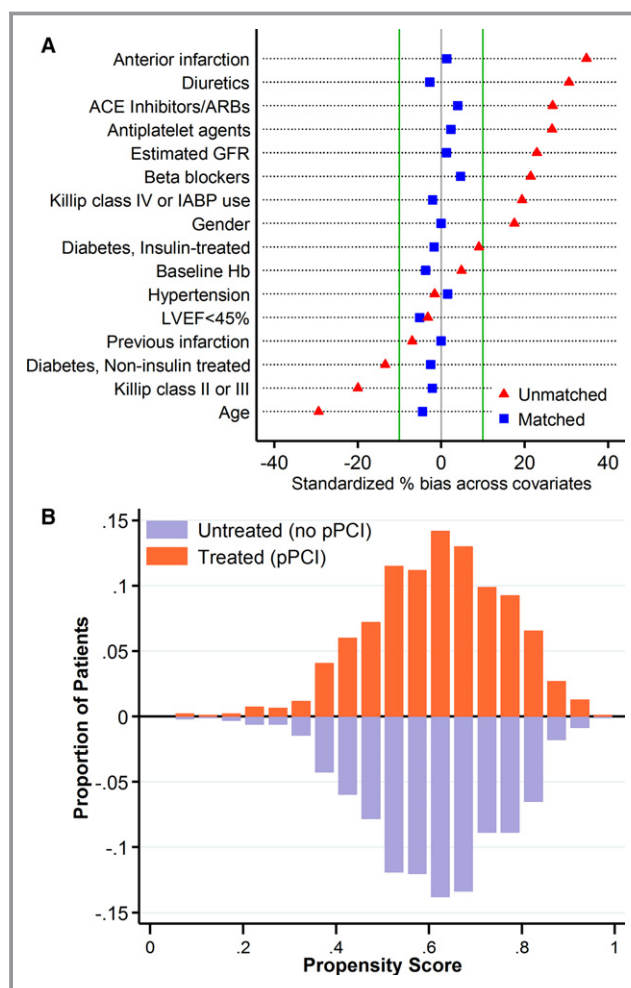
Figure 2. ROC curves of the simplified scoring model for acute kidney injury in the primary percutaneous coronary intervention (PCI) and thrombolysis/no reperfusion groups.

Figure 3. A, Covariable balance before (red triangles) and after (blue squares) matching. The standardized difference after propensity matching (blue squares) are all well within 10%. B, Mirrored histogram of distribution of propensity scores for primary percutaneous coronary intervention (pPCI; bars above the zero line) vs no-pPCI (bars below the zero line). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; Hb, hemoglobin; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction.
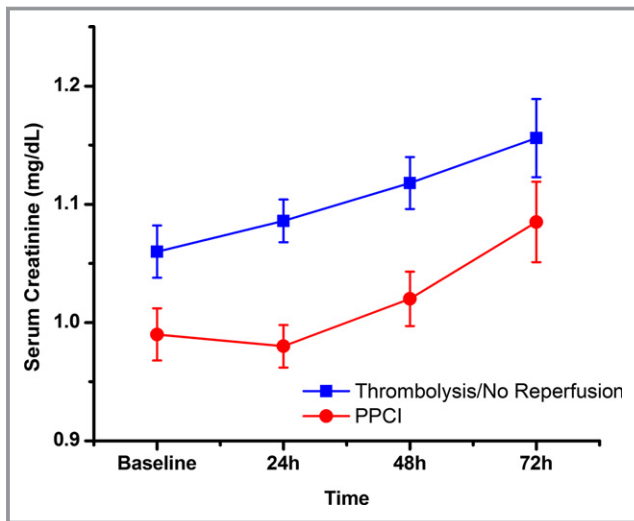
Figure 4. Fitted mean multivariate-adjusted trajectories of serum creatinine change over time in the primary percutaneous coronary intervention (pPCI) and thrombolysis/no reperfusion groups, based on the results from linear mixed models. The slops of the lines were similar (*P*=0.97 for interaction).

Discussion

The current analysis of STEMI patients undergoing pPCI and those treated with thrombolysis or without reperfusion provides no evidence that CM exposure is associated with increased rates of AKI. In an analysis of AKI events that accrued among propensity score–matched patients who were or were not exposed to CM, the rates of AKI were not significantly different. The slope of creatinine rise over the first 72 hours of hospitalization was similar in patients with and without CM exposure. AKI after pPCI was strongly

Figure 5. Cumulative incidence of mortality, readmission for heart failure, and recurrent myocardial infarction, according primary percutaneous coronary intervention (pPCI) treatment and occurrence of acute kidney injury (AKI).

associated with baseline eGFR, age, heart failure and hemodynamic instability, and reduced left ventricular function but not with contrast volume. Risk factors for AKI were similar among STEMI patients regardless of CM exposure. Finally, the use of a higher contrast dose was not associated with increased mortality rates, and AKI incurred similar risk for adverse events in patients with and without PCI.

In the radiology literature, <1% of all publications concerning CI-AKI had control groups.[9] These controlled studies demonstrated similar rates of AKI, dialysis, and death between patients in the groups that received CM and the control groups of patients who did not receive CM,[7,8] underscoring the crucial need for a control group of participants who do not receive CM.

To our knowledge, our study represents the first to include a control group of patients who were not exposed to CM in the setting of STEMI. We found that AKI occurred as frequently with and without CM exposure. A potential explanation for these findings is that there may be no appreciable increased risk of AKI associated with CM administration due to shared, and potentially more powerful, CM-independent risk factors for AKI in STEMI patients. Age, baseline renal dysfunction, and clinical evidence of heart failure or hemodynamic instability were major determinants of AKI risk in all STEMI patients. These results suggest CM-independent renal insults can explain most post-pPCI AKI events[14]; therefore, AKI in the setting of pPCI likely represents 1 facet of the spectrum of the type 1 cardiorenal syndrome.[15]

Animal models generally require that additional insults to the kidney be combined with contrast exposure to reliably induce AKI.[16] Similarly, in clinical studies including elective procedures performed on stable patients, the development of CI-AKI largely depends on coexisting risk factors such as intravascular volume depletion, baseline renal dysfunction, heart failure, and diabetes mellitus.[9]

The term *CI-AKI* implies impairment of renal function occurring within 3 to 5 days following the administration of CM in the absence of an alternative etiology[16,17]; however, it is unlikely that CM is the sole factor responsible for renal dysfunction in the patient population undergoing pPCI. Conditions resulting in low effective circulating volume, hypotension, hemodynamic instability or cardiogenic shock, acute heart failure, hemorrhage, and initiation of medical therapies are additional contributing factors that may lead directly to renal dysfunction or potentiate the effects of CM.[18] Consequently, in the setting of pPCI, most AKI events likely have alternative and multiple causes, and the use of the term *CI-AKI* in this context should be avoided in most cases.

The reported incidence of AKI is 1% to 3% in patients undergoing elective PCI[17,19–21] but rises significantly to 10% to 16% in patients undergoing pPCI.[3,22,23] The large increase in incident AKI is the result of heart failure, hemodynamic
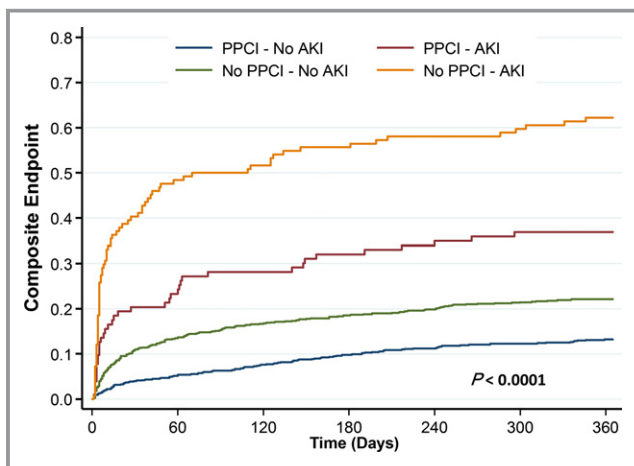
instability, and pharmacological interventions associated with STEMI rather than the use of greater contrast volume.

Unfortunately, the term CI-AKI is used frequently to describe AKI that occurs following an interventional procedure even when other potential explanations for AKI are present.[2,3,18] Because previous studies inherently lacked a control population of patients who did not receive CM, the relative contribution attributable to CM could not be extricated from CM-independent causes. Furthermore, potent risk factors that directly cause AKI such as IABP use in the setting of cardiogenic shock, are often cited as risk factors for CI-AKI.[18]

Few data are available with regard to risk factors for the development of AKI in patients undergoing pPCI. Our results are at odds with prior studies that reported a positive association between higher contrast volume and incident AKI in patients undergoing pPCI[2,3] although other risk factors for AKI were similar.[18] In contrast, as in the present study, Shacham and colleagues could not find an independent association between V/eGFR and AKI.[22] Furthermore, in randomized trials of complete versus lesion-only revascularization in patients undergoing pPCI, contrast volume was higher in the multivessel-PCI group with similar CI-AKI rates.[24,25] Recently, Kooiman reported that a high contrast dose (contrast volume [in ml] $\geq 3\times$ baseline eGFR) was only a marginal predictor of AKI after PCI, with an estimated attributable risk fraction to AKI of 10.6%.[14]

Although one cannot disagree with the need to avoid excess contrast volume in any patient undergoing pPCI, it is unlikely that CM is a primary pathogenic factor responsible for renal dysfunction in this patient population. Furthermore, the current results suggest that attempts to reduce AKI rates in STEMI patients likely require targeting mechanisms that are unrelated to CM.

AKI and Clinical Outcomes

The association between CI-AKI and adverse clinical outcomes, including cardiovascular complications and death, has been amply demonstrated in previous studies of patients with acute myocardial infarction.[26–28] These analyses, however, have not been sufficient to establish a causal relationship. More important, putative mechanisms for how CI-AKI increases cardiovascular events have not been elucidated.

In the present study, there was no significant association between contrast volume and mortality. AKI was strongly predictive of adverse outcomes; however, the impact of AKI on clinical outcomes was similar among patients with and without contrast exposure. These results suggest that contrast volume did not directly contribute to the increase in adverse events. Of note, risk variables that predicted mortality were also strong predictors of AKI. This overlap of risk factors for the development of AKI and for mortality is very common in the setting of pPCI, as many patients are

affected by cardiogenic shock, heart failure, and preexisting or acute renal failure.

Study Limitations

Some limitations of our study should be noted. Selection bias is an inherent concern in observational nonrandomized studies. Some patients were recruited during a period in which both pPCI and thrombolysis were acceptable reperfusion strategies. Consequently, treatment bias related to age, baseline renal function, infarct location, and hemodynamic status may have affected the decision to perform pPCI, resulting in heterogeneity caused by AKI-predisposing comorbidities between contrast and noncontrast groups. The use of propensity score matching cannot fully correct for these imbalances; therefore, the results should be viewed as exploratory and hypothesis generating only.

Because all patients in the present study underwent emergency PCI, no protocol-defined pre- or postprocedural hydration could be given. Total fluid volume and net fluid balance were not quantified in the study. Patients without heart failure may have been better hydrated, resulting in reduced incidence of AKI, although a recent study challenges the ability of hydration to prevent CI-AKI.[29]

Conclusion

In this study, the development of AKI in STEMI patients after pPCI is mainly related to older age, baseline eGFR, heart failure, and hemodynamic instability. Higher contrast was not associated with higher AKI or mortality rates. Risk of AKI is similar among STEMI patients with and without CM exposure.

Disclosures

None.

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