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Contrast-induced acute kidney injury following coronary angiography: a cohort study of hospitalized patients with or without chronic kidney disease

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ABSTRACT

Background. Contrast-induced acute kidney injury (CIAKI) has been linked to unfavorable consequences. In routine clinical practice, small increases in serum creatinine (SCr) following coronary angiography tend to be underestimated, especially in patients without chronic kidney disease (CKD).
Methods. We conducted a retrospective observational cohort study to analyze in-hospital and long-term outcomes of CIAKI following coronary angiography in patients with or without CKD (eGFR $\geq$ 60 mL/min/1.73 m^2) from January 2008 through December 2009. CIAKI was defined as SCr either $\geq$ 25% or $\geq$ 0.5 mg/dL from baseline within 72 h after contrast exposure. Multivariable logistic regression for in-hospital mortality and Cox proportional hazards calculations for long-term mortality and requirement for dialysis were performed.
Results. A total of 1160 patients were included in the study. CIAKI occurred in 19% of CKD patients and in 18% of non-CKD patients. In CKD and non-CKD patients, CIAKI was more frequent in patients requiring mechanical ventilation or inotropes or in those given furosemide, and it was associated with adverse in-hospital (prolonged hospitalization, acute dialysis and mortality) and long-term (increased creatinine, initiation of dialysis and mortality) outcomes. In multivariable analysis, CKD patients had greater in-hospital mortality if they developed CIAKI (adjusted OR 8, 95% CI 1.9–34.5, P = 0.005), and non-CKD patients had greater long-term mortality if they developed CIAKI (adjusted HR 2.2, 95% CI 1.2–4.1, P = 0.016).
Conclusions. CIAKI following coronary angiography was associated with adverse in-hospital and long-term outcomes in both CKD and non-CKD patients.

INTRODUCTION

Contrast-induced acute kidney injury (CIAKI) is a frequent cause of hospital-acquired acute kidney injury (AKI) in the USA [1] with an incidence that varies from 2% in low-risk populations [2] to 50% in high-risk patients [3]. CIAKI may be caused by sustained contrast-induced renal arteriolar vasoconstriction, outer medullary and tubular hypoxia or direct cytotoxicity due to ischemia-mediated oxidative stress [4]. Endothelin-1, adenosine, prostaglandins, vasopressin and nitric oxide have been described as potential mediators [4]. Risk factors for CIAKI are well defined and include hypotension, congestive heart failure, chronic kidney disease (CKD), diabetes, age > 75 years, anemia, large contrast volume and use of intra-aortic balloon pump (IABP) [2, 5]. However, preventive therapies [6–8], avoidance of nephrotoxic medications and the standardized use of low-osmolar or iso-osmolar contrast

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media [9, 10] have not consistently decreased the incidence of CIAKI. Likewise, different pharmacological approaches such as the use of fenoldopam, dopamine or captopril have not been invariably beneficial [3, 11, 12]. Only intravenous volume expansion has proven efficacy in attenuating the risk of CIAKI [13–15]. Unanswered questions include the utility of early urine or serum biomarkers [16], the effectiveness of periprocedural diuresis with matched hydration [17, 18], and the preferred choice of intravenous solution for volume expansion.

CIAKI has been linked to adverse in-hospital and long-term outcomes, including all-cause mortality and requirement for dialysis [2, 19–22]. Furthermore, some studies have shown significant associations between CIAKI and progression of CKD [21–23]. In contrast, other studies have not shown a relationship between CIAKI and progression of CKD or mortality following coronary angiography [24, 25], although in these studies, patients were relatively stable and underwent nonemergent angiography.

The primary aim of this study was to analyze in-hospital and long-term adverse outcomes following the occurrence of CIAKI in a cohort of hospitalized patients with or without CKD who underwent coronary angiography. A secondary aim was to determine whether chronic exposure to angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) constitute an independent predictor of CIAKI after coronary angiography.

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MATERIALS AND METHODS

Study design and participants

This study was a retrospective, observational cohort study of hospitalized patients with or without CKD. We utilized a population-based linked administrative database of patients admitted to Henry Ford Hospital, a tertiary care hospital, who underwent cardiac catheterization from January 2008 through December 2009. The original study population comprised 1725 hospitalized patients with various indications for cardiac catheterization. Patients with CKD stage 5, end-stage kidney disease and those exposed to other contrast medium or undergoing acute dialysis within 7 days prior to cardiac catheterization were excluded. Patients with incomplete or unknown ACEI or ARB exposure history or those exposed to both ACEI and ARB were also excluded. Patients were considered chronically exposed if they had been prescribed ACEI or ARB within 1 month of cardiac catheterization. We included cases of coronary angiography in which at least one value for serum creatinine (SCr) before and one value within 72 h after the procedure were available. A nonionic, iso-osmolar contrast medium (ioversol) was the sole contrast agent used. A sample of 1160 patients constituted our study cohort for the final analysis. Participants were followed for up to 34 months from the date of coronary angiography (mean 14 ± 8.6 months) until the study end date (28 February 2011) or death. The protocol was approved by the Institutional Review Board.

Study variables

The most recent SCr within the 6-month period before contrast exposure was defined as the baseline SCr and used to calculate the baseline estimated glomerular filtration rate (eGFR) based on the 4-variable Modification of Diet in Renal Disease (MDRD) study equation [26]. CKD patients were those with baseline eGFR <60 mL/min/1.73 m^2. The highest SCr within 72 h after the procedure was used to determine the occurrence of CIAKI.

CIAKI was defined as SCr either ≥ 25% or ≥ 0.5 mg/dL from baseline within 72 h after contrast exposure. This definition has been previously proposed and widely reported in the CIAKI literature [27–29].

Data pertaining to contrast volume, contrast ratio [contrast volume divided by maximum contrast dose (5 × body weight divided by SCr)] and the preventive strategy utilized by the interventional cardiologist were collected from the electronic records of the Cardiac Catheterization Laboratory. Comorbidity was identified using ICD-9-CM codes [30]. Data pertaining to periprocedural medications and intravenous fluids, intensive care unit (ICU) admission, ICU length of stay, hospital length of stay and use of IABP were based on hospital billing codes and review of electronic medical records.

Study outcomes

The impact of the occurrence of CIAKI on in-hospital outcomes, including all-cause mortality, acute dialysis and hospital length of stay, as well as long-term outcomes, including all-cause mortality, SCr increase ≥ 0.5 mg/dL (mean of the last two values within the follow-up period) and initiation of dialysis, were analyzed. Additionally, the influence of chronic therapy with ACEI or ARB on the development of CIAKI was estimated.

Statistical analysis

Microsoft Excel 2010 (Microsoft, Redmond, WA, USA) and SAS 9.2 (SAS Institute, Cary, NC, USA) were used for all data acquisition and analysis. Continuous variables were compared between groups using the two-sided *t*-tests. Between-group comparisons were made using Fisher's exact test or Chi-square analysis if none of the expected frequencies was <5. Kaplan–Meier graphs were constructed to estimate freedom from long-term mortality. The log-rank P-value given for each plot depicts the univariable association of CIAKI with mortality within that particular setting. Between-group comparisons were conducted with log-rank tests for censored data. Multivariable analysis was performed to adjust for known confounders that could influence the occurrence of CIAKI as well as other adverse outcomes [2, 5]. These variables consisted of demographic data (age, sex and gender), comorbidity (diabetes, hypertension, anemia and heart failure), baseline eGFR, indicators of critical illness (ICU admission, inotrope use, IABP and mechanical ventilation) and contrast medium volume and ratio for in-hospital and long-term outcomes. Data regarding the CIAKI prevention protocol utilized and periprocedural drug exposure were added in a logistic regression model to the already identified risk markers of

CIAKI [5] to determine the impact of ACEI or ARB on the occurrence of CIAKI following coronary angiography.

Multivariable analysis consisted of logistic regression for predictors of CIAKI, in-hospital mortality and SCr increase ≥0.5 mg/dL; linear regression for hospital length of stay; and Cox proportional hazards calculations for long-term dialysis initiation and mortality. Forest plots were constructed to compare mortality outcomes. The 95% confidence intervals reported for the logistic regression odds ratios and Cox regression hazard ratios were based on the Wald estimation. Statistical significance was set at an alpha level of 0.05.

RESULTS

The original study population comprised 1725 hospitalized patients with various indications for cardiac catheterization. After excluding patients who did not receive intra-arterial contrast or meet all of the inclusion criteria, 1160 patients remained. A total of 299 patients were excluded from the CKD group and 215 were excluded from the non-CKD group (baseline eGFR ≥60 mL/min/1.73m^2). Fifty-one patients were excluded because of incomplete data. Of the remaining 1160 patients, 457 (39%) had CKD and 703 (61%) had preserved kidney function at baseline. The mean time between the date of baseline SCr and the procedure date was 1.5 days for both CKD and non-CKD patients.

Characteristics of CKD and non-CKD patients are reported in Table 1. CIAKI occurred in 19% of CKD patients and in 18% of non-CKD patients. When only the absolute change in SCr (≥ 0.5 mg/dL from baseline) was used to define CIAKI, only 3% of non-CKD patients met criteria. CKD patients with CIAKI had lower baseline eGFR, more frequent anemia and greater exposure to contrast compared with those without CIAKI. In both CKD and non-CKD patients, CIAKI was associated with critical illness and exposure to inotropic agents or furosemide.

Independent predictors of CIAKI

In the logistic regression model, adjusting for possible confounders, several independent predictors of CIAKI were identified (Table 2). In CKD patients, independent predictors of CIAKI included periprocedural furosemide (given 24 h before or after the procedure), ICU admission, chronic exposure to ACEI or ARB, and baseline eGFR. In non-CKD patients, independent predictors of CIAKI included periprocedural sodium bicarbonate and furosemide, mechanical ventilation, ICU admission and female gender.

Study outcomes analysis

CIAKI was associated with adverse in-hospital outcomes in CKD and non-CKD patients. A total of 21 CKD patients (4.6%) and 9 non-CKD patients (1.3%) died during hospitalization. Those who developed CIAKI had a much higher risk of in-hospital mortality (Figure 1). Only four CKD patients (0.9%) and three non-CKD patients (0.4%) required acute dialysis, all of whom met criteria for CIAKI. CKD patients who developed CIAKI were hospitalized longer than those without CIAKI (9 ± 8.5 versus 6.1 ± 12.6 days, P < 0.001, respectively). Similarly, non-CKD patients with CIAKI were hospitalized longer than those without CIAKI (8.3 ± 13.5 versus 4.1 ± 5.6 days, P < 0.001, respectively).

CIAKI was also linked to adverse long-term outcomes in both groups. Of those who survived hospitalization, 385 of the 436 CKD patients and 542 of the 694 non-CKD patients were available for follow-up assessment (mean 15 and 13 months, respectively). The follow-up period was also similar for those who developed CIAKI and those who did not (mean 11 months for both groups). CKD and non-CKD patients who developed CIAKI following coronary angiography had greater risk of death, dialysis and worsening SCr compared with those who did not have CIAKI (Figure 2). Kaplan–Meier curves illustrate the time-dependent increases in mortality among CKD and non-CKD patients with or without CIAKI (log-rank P = 0.004 and <0.001, respectively) (Figure 3).

After adjustment for potential confounders, multivariable analysis identified CIAKI to be associated with adverse in-hospital and long-term outcomes. In CKD patients, CIAKI [adjusted odds ratio (OR) 8, 95% CI 1.9–34.5, P = 0.005], use of inotropic agents (P < 0.001) and mechanical ventilation (P < 0.001) were associated with in-hospital mortality (Figure 4). CIAKI predicted increases in SCr ≥ 0.5 mg/dL from baseline [adjusted hazard ratio (HR) 5.7, 95% CI 3.2–10.4, P < 0.001] and need for long-term dialysis (adjusted HR 9.1, 95% CI 2.5–32.8, P < 0.001). There was a nonsignificant trend toward an association of CIAKI with long-term mortality. In non-CKD patients, CIAKI was associated with long-term mortality (adjusted HR 2.2, 95% CI 1.2–4.1, P = 0.016) and predicted increases in SCr ≥0.5 mg/dL from baseline (adjusted HR 3.2, 95% CI 1.6–6.5, P = 0.001).

DISCUSSION

Our results demonstrate a strong association between CIAKI and adverse in-hospital and long-term outcomes in both CKD and non-CKD patients. Our study sample included hospitalized patients with diverse risk profiles for the development of CIAKI, although most patients received nonprotocolized intravenous volume expansion with isotonic saline, a measure that has been shown to reduce the risk of CIAKI [14]. Unique to our study is the separate analysis of CKD and non-CKD patients for independent predictors and outcomes. Furthermore, this study included a rarely examined cohort of non-CKD hospitalized patients undergoing coronary angiography, a group of patients in whom we tend to be less aggressive with preventive strategies and in whom we frequently underestimate small changes in SCr following contrast exposure.

Previously, CIAKI was thought to represent only a transient and clinically insignificant increase in SCr [31]. Although a causal relationship between CIAKI and deleterious outcomes cannot be confirmed by observational data, CIAKI should be considered a marker for adverse in-hospital and long-term outcomes following coronary angiography [32–34].

Table 1. Baseline characteristics

	CKD		P	Non-CKD		P
	Non-CIAKI ($n = 371$)	CIAKI ($n = 86$)		Non-CIAKI ($n = 573$)	CIAKI ($n = 130$)	
Age, years	68.4 ± 11.9	69.7 ± 10.5	0.35	59.0 ± 12.5	60.4 ± 12.4	0.25
Women	185 (50%)	48 (56%)	0.32	213 (37%)	66 (51%)	0.004
Race						
White	186 (50%)	46 (54%)	0.85	274 (48%)	57 (44%)	0.62
Black	140 (38%)	30 (35%)		225 (39%)	57 (44%)	
Other	45 (12%)	10 (12%)		74 (13%)	16 (12%)	
Chronic conditions						
Baseline SCr, mg/dL	1.57 ± 0.44	1.68 ± 0.61	0.25	0.97 ± 0.17	0.84 ± 0.20	<0.001
Baseline eGFR	46 ± 10	43 ± 12	0.02	85 ± 18	101 ± 38	<0.001
Diabetes	150 (40%)	36 (42%)	0.81	156 (27%)	35 (27%)	0.94
Anemia	220 (59%)	60 (70%)	0.07	202 (35%)	55 (42%)	0.13
Heart failure	34 (9%)	13 (15%)	0.1	37 (6%)	11 (8%)	0.41
Hypertension	153 (41%)	25 (29%)	0.04	396 (69%)	90 (69%)	0.98
CIAKI prevention						
IV normal saline	263 (71%)	58 (67%)	0.53	449 (78%)	99 (76%)	0.56
IV sodium bicarbonate	18 (5%)	11 (13%)	0.007	2 (0.3%)	4 (3%)	0.01
N-acetylcysteine	239 (64%)	53 (62%)	0.63	52 (9%)	14 (11%)	0.55
Periprocedural drugs						
Statin	269 (72%)	69 (80%)	0.14	460 (80%)	105 (81%)	0.9
Furosemide	164 (44%)	58 (67%)	<0.001	116 (20%)	49 (38%)	<0.001
NSAID	5 (1%)	0 (0%)	0.59	18 (3%)	3 (2%)	0.78
ACEI or ARB	248 (67%)	57 (66%)	0.92	440 (77%)	103 (79%)	0.55
Critical indicators						
ICU admission	117 (32%)	52 (60%)	<0.001	189 (33%)	71 (55%)	<0.001
Inotrope	35 (9%)	21 (24%)	<0.001	35 (6%)	17 (13%)	0.006
IABP	17 (5%)	11 (13%)	0.004	19 (3%)	9 (7%)	0.06
Mechanical ventilation	41 (11%)	27 (31%)	<0.001	43 (8%)	28 (22%)	<0.001
Contrast medium						
Contrast volume, mL	110 ± 83	136 ± 103	0.03	150 ± 108	136 ± 103	0.16
Contrast ratio	0.40 ± 0.32	0.51 ± 0.41	0.02	0.34 ± 0.25	0.30 ± 0.36	0.002

Categorical data are reported as frequencies (percent of group). Numerical data are reported as mean ± standard deviation. Abbreviations and definitions: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; contrast ratio, contrast volume administered divided by maximum contrast dose; eGFR, estimated glomerular filtration rate (4-variable Modification of Diet in Renal Disease equation, mL/min/1.73 m^2); IABP, intra-aortic balloon pump; ICU, intensive care unit; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; periprocedural, within 24 h before or after the procedure; SCr, serum creatinine.

Similar to our study, in which non-CKD patients had greater long-term mortality if they developed CIAKI, a population-based cohort study that included two-thirds of non-CKD subjects demonstrated a graded increase in long-term mortality following coronary angiography based on the severity of AKI by Acute Kidney Injury Network (AKIN) criteria

(2-fold increase in mortality rates for AKI stage 1 and >3-fold in those with AKI stage 2 or 3) [21]. In another observational study, CIAKI following coronary angiography occurred in 12.7% of non-CKD patients and was an independent predictor of 1-year mortality in this population [35]. Both of these studies highlighted the relevance of CIAKI in non-CKD patients in addition to the observed association of long-term mortality with small increases in SCr levels after acute myocardial infarction, independent of the baseline eGFR [36]. Furthermore, a recent systematic review and meta-analysis showed that even small increases in SCr levels (10 to 24% from baseline) in hospitalized patients are associated with twice the risk of short-term mortality [37]. It has been also observed that patients who survive AKI are at increased risk of long-term mortality and other adverse events compared with controls [38]. These findings are important, because therapeutic interventions such as optimization of volume status, avoidance of nephrotoxic drugs and early outpatient follow-up may be implemented in an attempt to improve survival, slow the progression of CKD and prevent hospital readmissions after an episode of AKI.

In patients who develop CIAKI, the observed excess in-hospital and short-term mortality has been attributed to cardiovascular complications or hemodynamic instability that requires IABP or vasoactive drugs [2, 35, 39]. Similarly, AKI has been described as an independent risk factor for 1-year mortality in patients with acute decompensated heart failure (e.g. cardiorenal syndrome type 1) [40] in relation to hemodynamic changes, venous renal congestion, neurohormonal activation of renin–angiotensin and sympathetic nervous systems and oxidative stress-mediated cellular injury [41]. CIAKI may thus identify patients with systemic and renal hemodynamic vulnerability, as was demonstrated in animal studies in which decreased vascular tone and increased vascular permeability were associated with organ dysfunction following ischemia–reperfusion injury [42, 43]. Conversely, CIAKI may directly contribute to the subsequent development of cardiovascular morbidity and mortality [2, 39, 44]. It should also be noted that our study comprised patients who underwent nonelective coronary angiography, had a mean hospital stay of 5 days and required ICU admission in at least one-third of cases. These characteristics make our cohort highly comparable to those of severely ill patients in which the occurrence of CIAKI adversely affected length of hospital stay and mortality [22, 45, 46].

Table 2. Independent predictors of CIAKI

	Odds ratio	95% CI
CIAKI in CKD patients		
ICU admission	2.75	1.64–4.59
Periprocedural furosemide	2.39	1.41–4.05
Chronic use of ACEI or ARB	2.38	1.35–4.20
Contrast ratio	2.28	1.15–4.51
Baseline eGFR	0.98	0.95–0.99
CIAKI in non-CKD patients		
IV sodium bicarbonate	14.09	1.85–107.17
Periprocedural furosemide	2.69	1.68–4.31
Mechanical ventilation	2.19	1.14–4.23
Women	2.11	1.36–3.27
ICU admission	2.03	1.26–3.27
Age	1.02	1.004–1.040

Stepwise logistic regression, including all of the parameters listed in Table 1. Abbreviations and definitions as listed in Table 1; chronic use of ACEI or ARB, use within 1 month prior to coronary angiography.

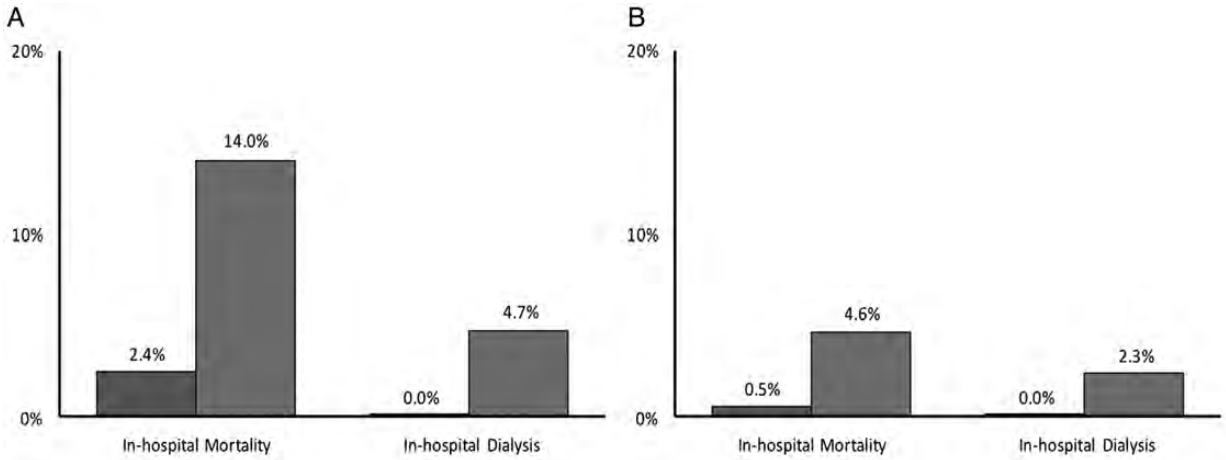

FIGURE 1: In-hospital outcomes of CIAKI following coronary angiography. (**A**) CKD patients and CIAKI. (**B**) Non-CKD patients and CIAKI. White bar, non-CIAKI; black bar, CIAKI. All comparisons $P < 0.01$.

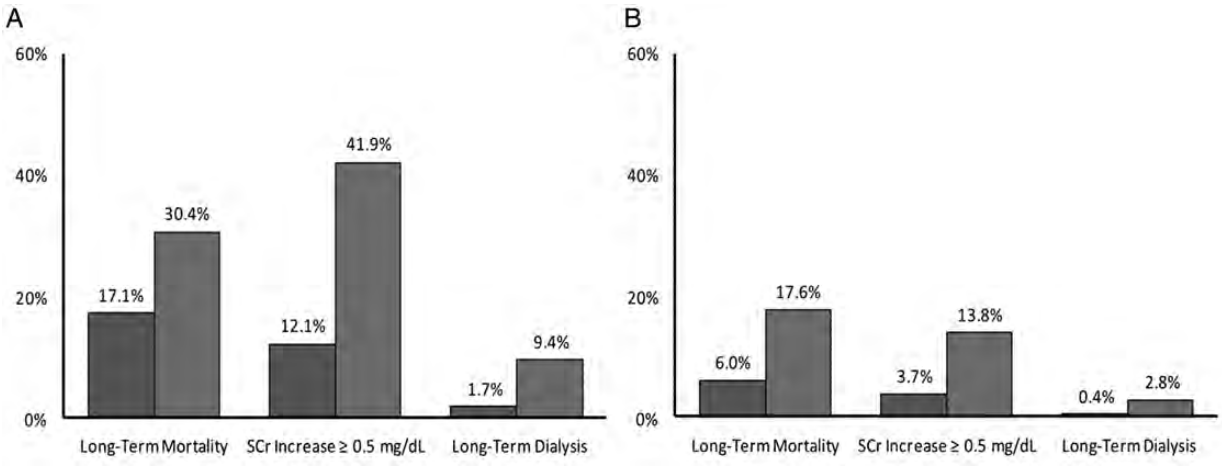

FIGURE 2: Long-term outcomes of CIAKI following coronary angiography. (**A**) CKD patients and CIAKI. (**B**) Non-CKD patients and CIAKI. White bar, non-CIAKI; black bar, CIAKI; SCr, serum creatinine (mg/dL). All comparisons $P < 0.015$.

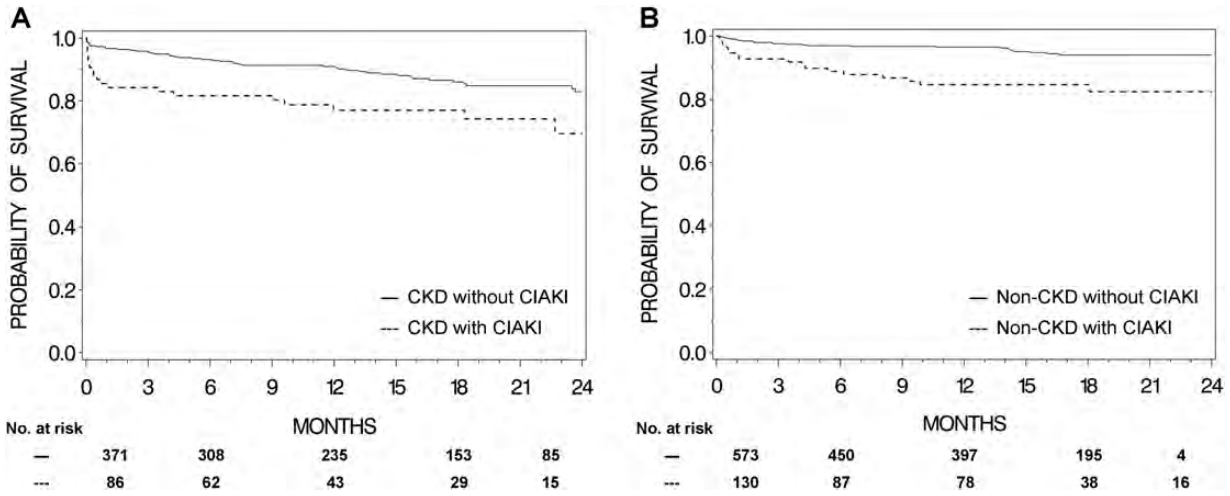

FIGURE 3: Kaplan–Meier cumulative mortality for occurrence of CIAKI. (**A**) CKD patients and CIAKI, log-rank $P = 0.004$. (**B**) Non-CKD patients and CIAKI, log-rank $P < 0.001$.

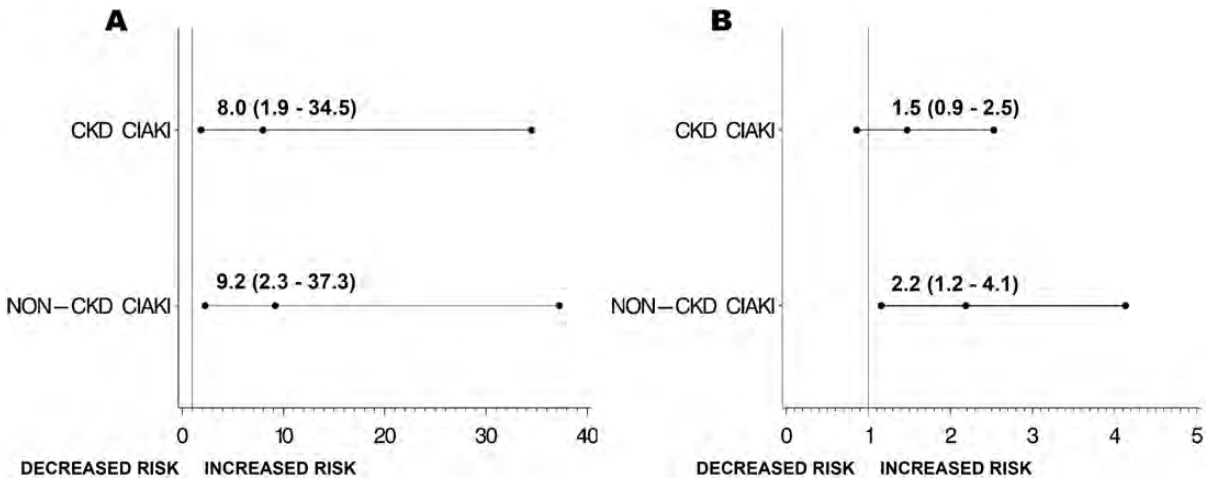

FIGURE 4: Multivariable analysis using CIAKI as a predictor of mortality. (**A**) Multiple logistic regression odds ratio estimates for in-hospital mortality. (**B**) Multiple Cox regression hazard ratio estimates for long-term mortality.

Recently, the emergent concept of subclinical AKI based on biomarkers of renal tubular injury (e.g. neutrophil gelatinase-associated lipocalin), even in the absence of significant decline in kidney function, has been associated with adverse outcomes, including mortality and dialysis following cardiac surgery [47]. The inclusion of these structural criteria of AKI (detection of biomarker without change in SCr) identified approximately 40% more cases in comparison with AKI by RIFLE criteria [47] and has been proposed as an update to the currently used definition of CIAKI [48]. As a decline in kidney function is typically evident only when more than 50% of nephron mass is compromised, minimal changes in SCr may not truly exclude underlying tubular damage, which may be linked to observed adverse outcomes.

In our study, CKD patients who were chronically exposed to ACEI or ARB were at higher risk for developing CIAKI. Although some investigators have implicated these agents as increasing the susceptibility to CIAKI [49–51], others have touted these same agents as protective [12]. Chronically damaged kidneys may be more vulnerable to ACEI- or ARB-mediated angiotensin II inhibition and consequent renal hemodynamic changes at the time of contrast exposure; hence, CKD patients may be more susceptible to CIAKI [49, 52]. Alternatively, chronic exposure to ACEI or ARB may identify a high-risk pool of patients with diabetes, kidney disease or heart disease who are at greater risk to develop CIAKI. In our study sample, patients who were chronically prescribed ACEI or ARB were older and more likely to have diabetes. It is not known whether withholding ACEI or ARB before coronary angiography prevents CIAKI. The current *Kidney Disease: Improving Global Outcomes (KDIGO)* guidelines for AKI state that there is insufficient evidence to recommend discontinuation of these medications prior to contrast administration [53], although no specific consensus opinion is given for high-risk patients.

Women without CKD were also at higher risk for developing CIAKI. Compared with men, women have increased cardiovascular mortality, especially after menopause [54]. Specifically, in-hospital mortality after coronary angiography is higher in women [55, 56], although in these cohorts, women were older and had a greater burden of comorbidity than men [57, 58]. CIAKI may be a factor in the relatively detrimental hospital course observed in women, although the reason for the higher incidence of CIAKI in women is unknown. Gender-specific responses to renal stimuli by contrast medium and the influence of ovarian hormones are possible explanations [55]. Furthermore, older women may have lower intrarenal medullary oxygenation [59], which may be linked to lower intrarenal medullary prostaglandin production [60], a potential risk factor for increased susceptibility to CIAKI. The increased risk of CIAKI in women may be also related to the contrast medium dose, namely a higher ratio of contrast volume to body surface area. In our study, women were older, more likely anemic and hypertensive, and exposed to furosemide more frequently than men. However, the increased risk of CIAKI in women persisted after multivariable adjustment for these factors. Our findings highlight the need to make evidence-based decisions regarding the risks and benefits of coronary angiography, notably by risk-stratification of women with respect to the development of CIAKI.

Periprocedural exposure to furosemide was significantly associated with CIAKI in our study cohort. Intravascular volume depletion is a risk factor for CIAKI, and exaggerated shifts in blood pressure can increase renal oxidative stress and also predispose to CIAKI [4, 5]. Thus, our data suggest that diuretics should be avoided in high-risk patients who are susceptible to volume depletion before contrast exposure. However, in cases of hypervolemia, such as acute decompensated heart failure, use of diuretics before contrast administration may help to optimize cardiac output and subsequent kidney perfusion, potentially decreasing the risk of CIAKI [4]. In our cohort of patients, the decision to continue or withhold furosemide before coronary angiography was based on the clinical judgment of the interventional cardiologist.

Non-CKD patients who had preventive sodium bicarbonate therapy were found to be at higher risk of CIAKI. This finding may be due to selection bias, as bicarbonate is commonly reserved for high-risk patients, although the potential effect of intracellular acidosis and tissue hypoxia induced by bicarbonate administration [61] may play a role in the pathogenesis of CIAKI. It should be noted that this result is difficult to interpret given the small number of patients who received this solution.

The strengths of our study include the utilization of a sample of susceptible hospitalized patients in which a sole contrast agent was used. Unique to our study is the analysis of outcomes and their predictors separately in CKD and non-CKD patients. We also tested the most commonly used definition of CIAKI, including absolute and relative changes in SCr from baseline. However, we do agree that there is a need for a unifying definition such as the AKIN criteria for all forms of AKI [53]. One potential limitation of our study includes the classification of all AKI events following coronary angiography as CIAKI. Although our data were insufficient to exclude other causes of AKI, such as ischemia or atheroembolism, the distinction among these alternate diagnoses is equally difficult in clinical practice and is unlikely to significantly affect patient management. In addition, because of the retrospective nature of our study, a causal association between risk factors and CIAKI was not established, the demonstration of which would require randomized, controlled trials.

In conclusion, our study identified numerous adverse in-hospital and long-term outcomes in patients who developed CIAKI following coronary angiography. In those with or without CKD, the occurrence of CIAKI conferred an increased risk of unfavorable events. It is especially important to avoid underestimating the significance of even a minimal increase in SCr ($\geq$ 25% from baseline) in patients with preserved kidney function, since these patients experience adverse outcomes and may benefit from risk stratification prior to coronary angiography.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis 2002; 39: 930–936
2. Bartholomew BA, Harjai KJ, Dukkipati S *et al.* Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. Am J Cardiol 2004; 93: 1515–1519
3. Kapoor A, Sinha N, Sharma RK *et al.* Use of dopamine in prevention of contrast induced acute renal failure—a randomised study. Int J Cardiol 1996; 53: 233–236
4. McCullough PA. Contrast-induced acute kidney injury. J Am Coll Cardiol 2008; 51: 1419–1428
5. Mehran R, Aymong ED, Nikolsky E *et al.* A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 2004; 44: 1393–1399
6. Solomon R, Deray G. How to prevent contrast-induced nephropathy and manage risk patients: practical recommendations. Kidney Int Suppl 2006; 100: S51–S53
7. Reddan D, Laville M, Garovic VD. Contrast-induced nephropathy and its prevention: what do we really know from evidence-based findings? J Nephrol 2009; 22: 333–351
8. Weisbord SD, Palevsky PM. Strategies for the prevention of contrast-induced acute kidney injury. Curr Opin Nephrol Hypertens 2010; 19: 539–549
9. Reed M, Meier P, Tamhane UU *et al.* The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv 2009; 2: 645–654
10. McCullough PA, Brown JR. Effects of intra-arterial and intravenous iso-osmolar contrast medium (iodixanol) on the risk of contrast-induced acute kidney injury: a meta-analysis. Cardiorenal Med 2011; 1: 220–234
11. Stone GW, McCullough PA, Tumlin JA *et al.* Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. JAMA 2003; 290: 2284–2291
12. Gupta RK, Kapoor A, Tewari S *et al.* Captopril for prevention of contrast-induced nephropathy in diabetic patients: a randomised study. Indian Heart J 1999; 51: 521–526
13. Solomon R, Werner C, Mann D *et al.* Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994; 331: 1416–1420
14. Mueller C, Buerkle G, Buettner HJ *et al.* Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med 2002; 162: 329–336
15. Brar SS, Shen AY, Jorgensen MB *et al.* Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. JAMA 2008; 300: 1038–1046
16. Briguori C, Visconti G, Rivera NV *et al.* Cystatin C and contrast-induced acute kidney injury. Circulation 2010; 121: 2117–2122
17. Briguori C, Visconti G, Focaccio A *et al.* Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury. Circulation 2011; 124: 1260–1269
18. Marenzi G, Ferrari C, Marana I *et al.* Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial. JACC Cardiovasc Interv 2012; 5: 90–97
19. McCullough PA, Wolyn R, Rocher LL *et al.* Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997; 103: 368–375
20. From AM, Bartholmai BJ, Williams AW *et al.* Mortality associated with nephropathy after radiographic contrast exposure. Mayo Clin Proc 2008; 83: 1095–1100
21. James MT, Ghali WA, Knudtson ML *et al.* Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. Circulation 2011; 123: 409–416
22. Wi J, Ko YG, Kim JS *et al.* Impact of contrast-induced acute kidney injury with transient or persistent renal dysfunction on long-term outcomes of patients with acute myocardial infarction undergoing percutaneous coronary intervention. Heart 2011; 97: 1753–1757
23. Solomon RJ, Mehran R, Natarajan MK *et al.* Contrast-induced nephropathy and long-term adverse events: cause and effect? Clin J Am Soc Nephrol 2009; 4: 1162–1169
24. Weisbord SD, Hartwig KC, Sonel AF *et al.* The incidence of clinically significant contrast-induced nephropathy following non-emergent coronary angiography. Catheter Cardiovasc Interv 2008; 71: 879–885
25. Inrig JK, Patel UD, Briley LP *et al.* Mortality, kidney disease and cardiac procedures following acute coronary syndrome. Nephrol Dial Transplant 2008; 23: 934–940
26. Levey AS, Bosch JP, Lewis JB *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130: 461–470
27. Jabara R, Gadesam RR, Pendyala LK *et al.* Impact of the definition utilized on the rate of contrast-induced nephropathy in percutaneous coronary intervention. Am J Cardiol 2009; 103: 1657–1662
28. Harjai KJ, Raizada A, Shenoy C *et al.* A comparison of contemporary definitions of contrast nephropathy in patients undergoing percutaneous coronary intervention and a proposal for a novel nephropathy grading system. Am J Cardiol 2008; 101: 812–819
29. Thomsen HS, Morcos SK. Contrast media and the kidney: European Society of Urogenital Radiology (ESUR) guidelines. Br J Radiol 2003; 76: 513–518
30. Waikar SS, Wald R, Chertow GM *et al.* Validity of International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Acute Renal Failure. J Am Soc Nephrol 2006; 17: 1688–1694

31. Conti CR. Contrast nephropathy or contrast creatininopathy. Clin Cardiol 2003; 26: 53–54
32. Mehran R, Brar S, Dangas G. Contrast-induced acute kidney injury. Underappreciated or a new marker of cardiovascular mortality? J Am Coll Cardiol 2010; 55: 2210–2211
33. Sterling KA, Tehrani T, Rudnick MR. Clinical significance and preventive strategies for contrast-induced nephropathy. Curr Opin Nephrol Hypertens 2008; 17: 616–623
34. Weisbord SD, Palevsky PM. Acute kidney injury: kidney injury after contrast media: marker or mediator? Nat Rev Nephrol 2010; 6: 634–636
35. Dangas G, Iakovou I, Nikolsky E *et al.* Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. Am J Cardiol 2005; 95: 13–19
36. Parikh CR, Coca SG, Wang Y *et al.* Long-term prognosis of acute kidney injury after acute myocardial infarction. Arch Intern Med 2008; 168: 987–995
37. Coca SG, Peixoto AJ, Garg AX *et al.* The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis. Am J Kidney Dis 2007; 50: 712–720
38. Coca SG, Yusuf B, Shlipak MG *et al.* Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 2009; 53: 961–973
39. Rudnick M, Feldman H. Contrast-induced nephropathy: what are the true clinical consequences? Clin J Am Soc Nephrol 2008; 3: 263–272
40. Bagshaw SM, Cruz DN, Aspromonte N *et al.* Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI Consensus Conference. Nephrol Dial Transplant 2010; 25: 1406–1416
41. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol 2012; 60: 1031–1042
42. Kingma JG Jr, Vincent C, Rouleau JR *et al.* Influence of acute renal failure on coronary vasoregulation in dogs. J Am Soc Nephrol 2006; 17: 1316–1324
43. Hassoun HT, Grigoryev DN, Lie ML *et al.* Ischemic acute kidney injury induces a distant organ functional and genomic response distinguishable from bilateral nephrectomy. Am J Physiol Renal Physiol 2007; 293: F30–F40
44. Go AS, Chertow GM, Fan D *et al.* Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351: 1296–1305
45. Marenzi G, Lauri G, Assanelli E *et al.* Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 2004; 44: 1780–1785
46. Wickenbrock I, Perings C, Maagh P *et al.* Contrast medium induced nephropathy in patients undergoing percutaneous coronary intervention for acute coronary syndrome: differences in STEMI and NSTEMI. Clin Res Cardiol 2009; 98: 765–772
47. Haase M, Devarajan P, Haase-Fielitz A *et al.* The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol 2011; 57: 1752–1761
48. Ronco C, Stacul F, McCullough PA. Subclinical acute kidney injury (AKI) due to iodine-based contrast media. Eur Radiol 2013; 23: 319–323
49. Cirit M, Toprak O, Yesil M *et al.* Angiotensin-converting enzyme inhibitors as a risk factor for contrast-induced nephropathy. Nephron Clin Pract 2006; 104: c20–c27
50. Kiski D, Stepper W, Brand E *et al.* Impact of renin-angiotensin-aldosterone blockade by angiotensin-converting enzyme inhibitors or AT-1 blockers on frequency of contrast medium-induced nephropathy: a post-hoc analysis from the Dialysis-versus-Diuresis (DVD) trial. Nephrol Dial Transplant 2010; 25: 759–764
51. Rim MY, Ro H, Kang WC *et al.* The effect of renin-angiotensin-aldosterone system blockade on contrast-induced acute kidney injury: a propensity-matched study. Am J Kidney Dis 2012; 60: 576–582
52. Schoolwerth AC, Sica DA, Ballermann BJ *et al.* Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. Circulation 2001; 104: 1985–1991
53. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int 2012; 2: 1–138
54. Roger VL, Jacobsen SJ, Pellikka PA *et al.* Gender differences in use of stress testing and coronary heart disease mortality: a population-based study in Olmsted County, Minnesota. J Am Coll Cardiol 1998; 32: 345–352
55. Iakovou I, Dangas G, Mehran R *et al.* Impact of gender on the incidence and outcome of contrast-induced nephropathy after percutaneous coronary intervention. J Invasive Cardiol 2003; 15: 18–22
56. Ma G, Yu D, Cai Z *et al.* Contrast-induced nephropathy in postmenopausal women undergoing percutaneous coronary intervention for acute myocardial infarction. Tohoku J Exp Med 2010; 221: 211–219
57. Kiski D, Stepper W, Breithardt G *et al.* Impact of female gender on frequency of contrast medium-induced nephropathy: post hoc analysis of dialysis versus diuresis trial. J Womens Health (Larchmt) 2010; 19: 1363–1368
58. Mueller C, Buerkle G, Perruchoud AP *et al.* Female sex and risk of contrast nephropathy after percutaneous coronary intervention. Can J Cardiol 2004; 20: 505–509
59. Prasad P, Epstein F. Changes in medullary pO2 during water diuresis as evaluated by blood oxygenation level dependent magnetic resonance imaging. Kidney Int 1999; 55: 294–298
60. Kuhlik A, Elahi D, Epstein F. Decline in urinary excretion of dopamine and PGE2 with age. Ger Nephrol Urol 1995; 5: 79–83
61. Mathieu D, Neviere R, Billard V *et al.* Effects of bicarbonate therapy on hemodynamics and tissue oxygenation in patients with lactic acidosis: a prospective, controlled clinical study. Crit Care Med 1991; 19: 1352–1356

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