Impact of contrast-induced acute kidney injury on the association between renin-angiotensin system inhibitors and long-term mortality in heart failure patients

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Abstract

Introduction: Renin-angiotensin system inhibitors (RASi) reduce mortality among heart failure (HF) patients, but their effect among those complicating contrast-induced acute kidney injury (CI-AKI) remains unexplored. We aimed to investigate whether the relationship between RASi prescription at discharge and mortality differs between HF patients with or without CI-AKI following coronary angiography (CAG).

Methods: About 596 HF patients from an observational cohort were divided into a CI-AKI group ($n = 104$) and a non-CI-AKI group ($n = 492$) based on whether they had CI-AKI following CAG. The endpoint was all-cause mortality. Multivariable Cox regression was performed in each group to explore the associations between RASi at discharge and mortality.

Results: During the median follow-up time of 2.26 (1.70; 3.24) years, higher mortality rate was observed in the CI-AKI group compared to the non-CI-AKI group (18.3% vs 8.9%, $p = 0.002$). Among HF patients with CI-AKI, after adjusting

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for confounding factors, the association was not significant between RASi prescription at discharge and mortality (HR: 0.39, 95%CI: 0.12–1.31, $p = 0.128$), while it was among those without CI-AKI (HR: 0.39, 95%CI: 0.18–0.84, $p = 0.016$). **Conclusion:** RASi prescription at discharge for HF patients complicating CI-AKI tended to be ineffective, while it benefited those without CI-AKI. Further randomized evidence is needed to confirm this trend.

Introduction

Patients with heart failure (HF) have a high risk of developing contrast-induced acute kidney injury (CI-AKI), which is associated with an increased mortality rate.[1–5] Although renin-angiotensin system inhibitors (RASi), particularly angiotensin-converting enzymes inhibitors (ACEI) or angiotensin-receptor blockers (ARB), have been proven to be effective in reducing mortality among HF patients,[6,7] they are always reduced/discontinued during acute episodes of which acute kidney injury (AKI) accounts for about 55.4%–56.7%.[8,9] Since this reduction/discontinuation due to the concern about worsening impaired renal function is based on limited evidence, questions have arisen as to the appropriateness of not prescribing such patients RASi.[10–12] Recently, several studies have investigated the association between RASi treatment at discharge and long-term mortality among patients in the intensive care unit (ICU) complicating AKI, but the results were inconsistent,[13–15] and whether RASi prescription for patients with HF complicating CI-AKI can still improve prognosis remains unexplored. Therefore, the objective of this study was to investigate whether the relationship between RASi prescription at discharge and long-term mortality differs between HF patients with or without CI-AKI following coronary angiography (CAG).

Materials and methods

Patients

The association between RASi and long-term mortality was explored among 596 patients with HF (defined as left ventricular ejection fraction (LVEF) < 40% or New York Heart Association (NYHA) class > II/Killip class > I) undergoing CAG or percutaneous coronary intervention (PCI) between January 2010 to December 2013 at Guangdong Provincial Institute of Cardiovascular Diseases, Guangdong Provincial People's Hospital. The exclusion criteria included contrast media injection within the previous 7 days or 3 days post-operation, CAG with high or iso-osmolarity contrast agents, pregnancy or lactation, cardiovascular surgery, end-stage renal dysfunction,

or renal transplantation, missing of preoperative or postoperative creatinine, malignant tumors, and no hydration.[16] This study was conducted according to the principles of the Declaration of Helsinki and was approved by the ethics committee of the Guangdong Provincial People's Hospital. All the patients enrolled in this study signed written informed consent.

Endpoint and definitions

The endpoint of this study was all-cause mortality. All eligible patients included in this study were followed up through office visits or telephone interviews at 1, 6, 12, 24, 36, and 48 months after enrollment. CI-AKI was defined as Scr elevation > 25% or 0.5 mg/dL from baseline within the first 48 to 72 h after CAG. Patients who were prescribed ACEI or ARB at discharge were defined as RASi treated at discharge. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73*m^2 (calculated by the modification of diet in renal disease formula).

Interventions

The procedures were performed by an experienced cardiovascular team and followed standard clinical practice guidelines. The use of RASi, diuretics, beta blockers, or other non-invasive treatment strategies of patients was determined by the care provider based on the usual standard of care recommended in the published guidelines and recorded carefully.

Statistical analyses

All the enrolled patients were divided into two independent groups, the CI-AKI group ($n = 104$) and the non-CI-AKI group ($n = 492$), according to whether they had CI-AKI following CAG. Then, we explored the relationship between RASi prescriptions and all-cause mortality in these two groups, respectively. For continuous variables with normal distribution, two independent sample *t*-tests were performed [expressed as mean ± standard deviation

(SD)]. And Wilcoxon rank-sum test was used for continuous variables with non-normal distribution (expressed as median and IQR). Pearson's chi-square or Fisher's exact test was performed on the categorical data (expressed as a percentage), as appropriate. In addition, a comparison of the incidence of events between groups and survival analysis was performed. Potential risk factors including age, systolic blood pressure (SBP), acute myocardial infarction (AMI), CKD, LVEF < 40, beta blockers during hospitalization, and RASi at admission were selected clinically and based on a previous study.[14] Multivariable COX regression analysis adjusting for the potential risk factors was conducted in the CI-AKI group and the non-CI-AKI group respectively, in order to determine whether RASi prescription at discharge was associated with all-cause mortality. We also made an additional analysis. Patients prescribed with RASi at discharge were then further treated as an unordered categorical variable which included patients with ACEI at discharge, patients with ARB at discharge and patients without ACEI/ARB at discharge. Multivariable COX regression analysis and survival analysis were conducted to explore whether the result is consistent between patients with ACEI and patients with ARB. Missing data was not imputed. $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using R software (version 3.6.1; R core team, Vienna, Austria).

Results

Patients characteristics

Details of patient characteristics according to whether they had CI-AKI are provided in Supplemental Table 1. Table 1 details patient characteristics of the CI-AKI group and the non-CI-AKI group respectively based on the RASi treatment at discharge.

Among the 104 HF patients complicated with CI-AKI, 76 of them were treated with RASi at discharge while the others were not. In this CI-AKI group, patients who did not have RASi prescriptions at discharge were more likely to be diagnosed with CKD (53.6% vs 26.3%) and LM lesions (32.1% vs 12.8%) compared to those who did have prescriptions. Moreover, they were less likely to take RASi at admission.

Furthermore, of the 492 HF patients without CI-AKI following CAG, 416 were treated with RASi at discharge. In this non-CI-AKI group, patients who did not have RASi prescriptions at discharge were more likely to be emaciated (60 kg vs 63 kg) and diagnosed with diabetes (36.8% vs 25.7%) and experienced PCI (21.1% vs 12.3%) compared to those who did. They also tended to have lower systolic blood pressure (119.5 mmHg vs 125.0 mmHg) and less hypertension (34.2% vs 57.9%) and RASi at admission (51.3% vs 94.5%). In addition, in both groups, the proportion of post-procedure dialysis in patients who did not have RASi prescriptions at discharge was much higher than those who did have prescriptions (Table 2).

Association of CI-AKI and all-cause mortality among HF patients

During the median follow-up time of 2.26 (1.70; 3.24) years, mortality was 10.6% ($n = 63$) in total, 18.3% ($n = 19$) in the CI-AKI group, and 8.9% ($n = 44$) in the non-CI-AKI group ($p = 0.002$). Patients who had CI-AKI following CAG suffered a higher mortality rate (Supplemental Figure 1; Log-rank $p = 0.0058$).

Impact of RASi prescription at discharge on all-cause mortality

For subjects in the non-CI-AKI group, a lower mortality rate was observed in patients who had RASi at discharge compared to those who did not (7.7% vs 15.8%, Figure 1, Log-rank $p = 0.0175$). Meanwhile, in the CI-AKI group, patients prescribed with RASi at discharge also demonstrated a lower mortality rate compared to those who were not (13.2% vs 32.1%, Figure 1, Log-rank $p = 0.0073$).

After adjusting for prognostic variables including age, SBP, AMI, CKD, LVEF < 40, beta blockers during hospitalization and RASi at admission, RASi prescription at discharge was significantly associated with lower mortality in the non-CI-AKI group (HR: 0.39, 95% CI: 0.18–0.84, Table 3). However, this association was not maintained among patients in the CI-AKI group, with a hazard ratio of 0.39 and 95% confidence interval of 0.12–1.31 (Table 3).

In additional analysis, after adjusting for prognostic variables, both ACEI prescription and ARB prescription at discharge were not associated with lower mortality in the CI-AKI group. However, in the non-CIAKI group, ACEI prescription at discharge was associated with lower mortality (HR: 0.36, 95%CI: 0.16–0.80, $p = 0.013$) while ARB prescription at discharge was not (HR: 0.49, 95%CI: 0.19–1.29, $p = 0.151$) (Supplemental Table 2). Survival analysis demonstrated that ACEI may benefit HF patients complicating CI-AKI, while ARB did not. Similar result was also observed in HF patients without CI-AKI (Supplemental Figure 2).

Discussion

The present study was the first prospective observational study to explore the impact of CI-AKI on the association between RASi and the long-term mortality rate among patients with heart failure. After adjusting for prognostic factors, RASi prescription at discharge was significantly associated with decreased all-cause mortality among HF patients without CI-AKI but not among those with CI-AKI,

Table 1. Baseline characteristics of heart failure patients with or without contrast-induced acute kidney injury according to their RASi treatment at discharge.

	CI-AKI			Non-CI-AKI		
	No RASi at discharge (n = 28)	RASi at discharge (n = 76)	p value	No RASi at discharge (n = 76)	RASi at discharge (n = 416)	p value
Age, y	71.0 (65.8; 75.3)	73.0 (61.8; 77.0)	0.797	66.0 (57.5; 73.0)	66.0 (56.0; 73.0)	0.782
Male sex, n (%)	22 (78.6)	53 (69.7)	0.373	56 (73.7)	321 (77.2)	0.510
Weight, kg	60.0 (55.6; 67.6)	60.5 (55.8; 70.0)	0.786	60.0 (54.8; 70.0)	63.0 (57.9; 70.0)	0.019
SBP, mmHg	125.0 (102.8; 131.5)	126.5 (113.0; 138.3)	0.310	119.5 (103.8; 133.3)	125.0 (112.0; 139.0)	0.020
DBP, mmHg	70.0 (64.5; 78.0)	75.0 (66.0; 80.0)	0.169	74.0 (63.8; 80.0)	75.0 (68.0; 83.0)	0.141
LVEF	41.5 (35.3; 51.8)	46.0 (38.0; 58.8)	0.099	45.5 (36.0; 54.5)	41.0 (34.0; 59.0)	0.778
LVEF <40, %	12 (42.9)	24 (31.6)	0.210	26 (34.2)	185 (44.5)	0.177
Hypertension, n (%)	15 (53.6)	55 (72.4)	0.070	26 (34.2)	241 (57.9)	<0.001
CKD, n (%)	15 (53.6)	20 (26.3)	0.009	23 (30.3)	131 (31.5)	0.832
Diabetes, n (%)	8 (28.6)	24 (31.6)	0.768	28 (36.8)	107 (25.7)	0.046
AMI, n (%)	17 (60.7)	53 (69.7)	0.384	41 (53.9)	192 (46.2)	0.218
IABP, n (%)	2 (7.1)	1 (1.3)	0.159	2 (2.6)	5 (1.2)	0.291
PCI, n (%)	7 (25.0)	34 (44.7)	0.068	16 (21.1)	51 (12.3)	0.040
LM lesion, n (%)	9 (32.1)	10 (12.8)	0.026	12 (15.8)	66 (15.9)	0.960
CM dose, mL	115.0 (77.5; 153.8)	145.0 (97.5; 171.3)	0.103	100.0 (80.0; 150.0)	130.0 (80.0; 170.0)	0.183
Diuretics, n (%)	15 (53.6)	35 (46.1)	0.496	27 (35.5)	162 (38.9)	0.630
Statin, n (%)	26 (92.9)	73 (96.1)	0.610	74 (97.4)	395 (95.0)	0.555
Beta-blocker, n (%)	19 (67.9)	51 (67.1)	0.942	58 (76.3)	340 (81.7)	0.251
CCB, n (%)	4 (14.3)	11 (14.5)	1.000	6 (7.9)	48 (11.5)	0.364
RASi at admission, n (%)	19 (67.9)	69 (90.8)	0.011	39 (51.3)	393 (94.5)	<0.001
SCr at admission, mmol/L	109.4 (81.5–154.0)	83.5 (65.0–102.3)	<0.001	98.0 (78.7; 123.3)	92.7 (79.1; 112.2)	0.387
SCr peak after CAG, mmol/L	211.6 (130.3; 300.0)	119.5 (94.8; 154.1)	<0.001	94.0 (80.2; 123.0)	96.0 (80.0; 114.0)	0.541

RASi: renin-angiotensin system inhibitors; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; CKD: chronic kidney disease; AMI: acute myocardial infarction; IABP: intra-aortic balloon pump; PCI: percutaneous coronary intervention; LM: left main coronary artery; CM: contrast medium; PPI: proton pump inhibitors; CCB: calcium channel blocker; AHF: acute heart failure; SCr: serum creatinine; CAG: coronary angiography.

Table 2. In-hospital events of heart failure patients with or without CI-AKI based on their RASi treatment at discharge.

Events	CI-AKI			Non-CI-AKI		
	Non-RASi group (n = 28)	RASi group (n = 76)	p value	Non-RASi group (n = 76)	RASi group (n = 416)	p value
Post procedure dialysis, n (%)	5 (17.86)	1 (1.32)	0.005	3 (3.9)	1 (0.2)	0.013
Arrhythmia, n (%)	5 (17.86)	5 (6.58)	0.128	3 (3.9)	15 (3.6)	0.749
AHF, n (%)	5 (17.86)	11 (14.47)	0.761	5 (6.6)	17 (4.1)	0.362

RASi: renin-angiotensin system inhibitors; AHF: acute heart failure.
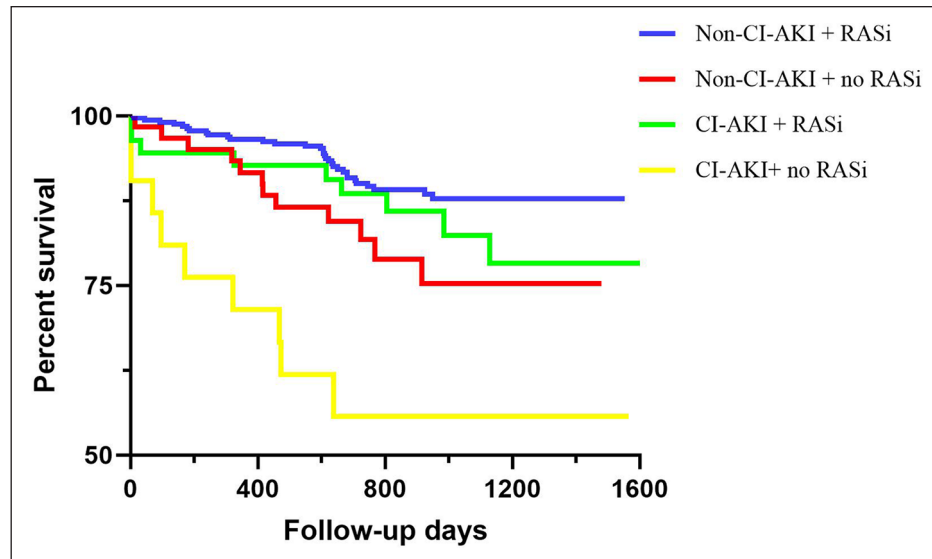
Figure 1. Association between prescription of RASi at discharge and all-cause mortality in HF patients with or without CI-AKI. CI-AKI: contrast-induced acute kidney injury; RASi: renin-angiotensin system inhibitors.

which suggests a trend that treatment with RASi at discharge among HF patients may not improve prognosis while they are experiencing CI-AKI.

In the current study, CI-AKI was observed to be associated with worse prognosis among HF patients. This finding was similar to the previous studies,[5,17,18] and the association may be due to progressive kidney disease, hypertension, stroke, or cardiovascular events following this acute renal episode.[19]

Meanwhile, we also observed there to be a significant association between RASi treatment at discharge and an improved prognosis among HF patients without CI-AKI. In daily practice, RASi prescription is recommended as a cornerstone of secondary prevention of HF as it is effective in reducing mortality,[6,7] with some randomized controlled trials having proven this protective effect.[20,21]

However, in our current study, the suggested protective effect was not significant among HF patients with CI-AKI, and this finding was an echo of the clinical dilemma of whether physicians should prescribe RASi when their patients are experiencing CI-AKI. Similar results had also been observed in other studies. Scarton et al.[15] performed

an ancillary of the AKIKI trial, and included 348 ICU patients with severe AKI (KDIGO stage 3). After adjustment for prognostic variables, mortality risk was not associated with RASi treatment at discharge (HR: 1.71, 95% CI 0.71–3.90).[15] Wang et al.[13] performed an ancillary of the RENAL study, including 1508 patients in ICU with AKI deemed to require renal replacement therapy and found that the protective effect of ACEI administration was not significant (HR: 0.78, 95% CI 0.51–1.21) using a time-dependent analysis. Such a negative result was also observed by Berra et al.[17] in a retrospective cohort study of 153 patients hospitalized for acute heart failure who had developed worsening renal function.

The insignificant association between RASi prescription at discharge and long-term mortality among HF patients with CI-AKI may be due to the following reasons. First, patients with impaired heart function are prone to have insufficient renal blood flow. RASi can lower glomerular hydrostatic pressure and decrease GFR by inhibiting of efferent renal arteriolar resistance, and these effects are more evident after diuresis.[22–24] Second, renal excreted drugs including contrast media and low molecular weight heparin during the procedure/digoxin as a

Table 3. Univariable and multivariable analysis of potential risk factors for all-cause mortality among HF patients with or without contrast-induced acute kidney injury.

	CI-AKI				Non-CI-AKI			
	Univariable analysis	*p* value	Multivariable analysis	*p* value	Univariable analysis	*p* value	Multivariable analysis	*p* value
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
RASi at discharge	0.34 (0.14–0.84)	0.019	0.39 (0.12–1.31)	0.128	0.66 (0.30–1.49)	0.323	0.39 (0.18–0.84)	0.016
Age	1.05 (1.00–1.11)	0.064	1.04 (0.97–1.10)	0.263	1.02 (0.99–1.05)	0.121	1.03 (0.99–1.06)	0.166
SBP	0.99 (0.96–1.01)	0.201	0.98 (0.96–1.00)	0.111	1.00 (0.99–1.02)	0.862	1.00 (0.99–1.02)	0.957
DBP	0.97 (0.93–1.02)	0.197			1.01 (0.99–1.04)	0.234		
AMI	0.92 (0.35–2.43)	0.864	1.13 (0.35–3.70)	0.835	1.07 (0.59–1.94)	0.822	1.84 (0.96–3.52)	0.066
CKD	4.21 (1.39–12.69)	0.011	2.17 (0.64–7.39)	0.215	2.74 (1.41–5.32)	0.003	2.44 (1.23–4.81)	0.010
LVEF <40	0.69 (0.25–1.91)	0.471	0.85 (0.25–2.92)	0.801	2.45 (1.30–4.60)	0.006	3.36 (1.71–6.60)	<0.001
IABP	3.20 (0.41–24.81)	0.266			3.93 (0.95–16.29)	0.059		
BB during hospitalization	0.33 (0.14–0.82)	0.017	0.30 (0.10–0.89)	0.030	0.55 (0.29–1.05)	0.07	0.53 (0.26–1.10)	0.088
Diuretic	0.63 (0.29–1.33)	0.225			2.11 (1.16–3.84)	0.014		
RASi at admission	0.43 (0.14–1.31)	0.140	1.14 (0.30–4.26)	0.847	0.66 (0.30–1.49)	0.323	1.13 (0.41–3.08)	0.814

HR: hazard ratio; CI: confidence interval; RASi: renin-angiotensin system inhibitors; SBP: systolic blood pressure; DBP: diastolic blood pressure; CKD: chronic kidney disease; IABP: intra-aortic balloon pump; BB: beta blockers.

routine treatment strategy may accumulate in patients with acute renal impairment.[6]

In the additional analysis, we seem to observed a better protecting effect of ACEI than that of ARB. Similar result has been reported by a recent study. Kim et al.[25] enrolled 23,978 patients with AMI who underwent successful PCI and found that the relative risk of major adverse cardiac events was higher in the BB + ARB group than in the BB + ACEI group after propensity score-matched (PSM) analysis. However, in our study, we must noticed that the number of patients prescribed with ARB is only one third of that of patients prescribed with ACEI. The result must be interpreted with caution.

Although we observed no protective effect of RASi in patients with HF complicating CI-AKI, we did, on the other hand, observe no harm relating to the RASi prescription and confirmed the safety and rationality of further randomized control trials.

However, the current finding of this study must be interpreted cautiously as several limitations occurred in this study. First, it was an observational study, and the treatment allocation might have been affected by many confounding factors. To reduce the selection bias, we have adjusted for the most critical factors, including RASi treatment at admission, CKD, LVEF, and age. Second, we were unable to evaluate the RASi treatment adherence, which might have potentially affected the result, although we reminded the patients of drug adherence during each interview. Third, since the patients were enrolled between 2010 and 2013 when angiotensin receptor–neprilysin inhibitor (ARNI) were not widely available in China, we did not have sufficient data regarding ARNI which is a new treating strategy for HF patients. Finally, our results may be affected by the relatively small sample size, though this cohort was derived from an extensive database, including 3469 patients undergoing CAG (PREdictive Value of COntrast voluMe to creatinINe Clearance Ratio, [PRECOMIN], ClinicalTrials.gov Identifier: NCT01400295).

Conclusion

Among HF patients without CI-AKI, RASi prescription at discharge was significantly associated with a better prognosis. However, among those with CI-AKI, the association between RASi prescription at discharge and mortality tended to be insignificant. Our preliminary finding of this trend warrants the performance of randomized controlled trials investigating the impact of RASi at discharge on the prognosis among patients with HF complicating CI-AKI.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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