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Incidence, Risk Factors and Prognosis of Contrast-Induced Acute Kidney Injury in Acute Heart Failure Patients Undergoing Coronary Angiography

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ABSTRACT

Background and Objectives: Heart failure (HF) is a well-known risk factor for contrast-induced acute kidney injury (CI-AKI). We sought to evaluate the risk factors and prognostic impact of CI-AKI in patients with AHF who undergo coronary angiography (CAG).

Methods: A total 594 patients with AHF underwent CAG from May 1, 2011 to December 31, 2013. CI-AKI was defined as an increase $\geq 25\%$ or ≥ 0.5 mg/dL in serum creatinine at 48 hours after CAG or the initiation of dialysis after CAG. The deviation of body weight on CAG day from the dry weight ($\Delta\text{BWT}_{\text{CAG}}$, %) was calculated for each patient.

Results: Overall, CI-AKI was observed in 24.7% of patients. Patients with CI-AKI had higher in-hospital death (16.3% vs. 5.1%, $p < 0.001$; relative risk [RR], 2.50; 95% confidence interval [CI], 1.45–4.31) and 1-year post-discharge death (38.1% vs. 17.4%, $p < 0.001$; hazard ratio, 2.16; 95% CI, 1.40–3.34) than those without CI-AKI. Patients with CI-AKI had greater $\Delta\text{BWT}_{\text{CAG}}$ than those without CI-AKI ($5.5 \pm 5.7\%$ vs. $3.7 \pm 4.0\%$, $p < 0.001$). A J-shaped association between the risk of CI-AKI and $\Delta\text{BWT}_{\text{CAG}}$ was noted. In patients with weight excess ($n = 179$), an increase of ΔBWT by 1% was associated with 9% (RR, 1.09; 95% CI, 1.03–1.16), while in patients with weight deficiency ($n = 86$), a decrease of ΔBWT by 1% was associated with 11% increased risk for CI-AKI (RR, 1.11; 95% CI, 1.05–1.17).

Conclusions: In AHF patients undergoing CAG CI-AKI is common and associated with worse clinical outcomes. Achieving optimum body weight before CAG may reduce the risk of CI-AKI.

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Trial Registration

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

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Keywords: Acute heart failure; Contrast media; Acute kidney injuries; Body weight

INTRODUCTION

Acute heart failure (AHF) is the leading cause of hospitalization worldwide.^{1,2)} Because more than 50% of AHF cases have ischemic etiology,³⁾ guidelines underscore the importance of timely evaluation of ischemia.^{4,7)} In case of suspicious ischemic cardiomyopathy, performing coronary angiography (CAG) is reasonable to find patients eligible for revascularization.

Contrast-induced acute kidney injury (CI-AKI) is an acute kidney injury that occurs after the administration of contrast media during CAG.⁸⁾ Although the majority of CI-AKI cases resolve spontaneously, sometimes grave consequence can follow such as permanent loss of kidney function or even death.⁹⁾ Heart failure is a well-known risk factor for CI-AKI.^{9,10)} Hypothetically, both systemic congestion, especially at admission, and volume depletion after over-diuresis can result in decreased renal perfusion in patient with AHF.^{11,13)}

No previous study has specifically examined the incidence, risk factors and clinical impact of CI-AKI in patients with AHF who represent the truly high-risk patients. In this study we had 2 main objectives. The first objective was to evaluate the incidence and clinical impact of CI-AKI in AHF patients undergoing CAG. Identification of risk factors allows the prediction of CI-AKI risk and may further highlight modifiable factors to minimize the risk of kidney injury in these vulnerable patients. Therefore, the second objective was to find clinical and procedural factors associated with the risk of CI-AKI in patients with AHF undergoing CAG.

METHODS

Study population

This study is a post hoc analysis of the Korean Acute Heart Failure (KorAHF) registry (ClinicalTrial.gov, [NCT01389843](#)).^{14,15)} From May 1, 2011 to December 31, 2013, all consecutive patients with AHF were prospectively enrolled at 3 tertiary hospitals (Seoul National University Bundang Hospital, Seoul National University Hospital, and Samsung Medical Center). These are patients with signs or symptoms of heart failure (HF) and either lung congestion, objective findings of left ventricle (LV) systolic dysfunction, or structural heart disease. Patients with HF were categorized into the heart failure with reduced ejection fraction (HFrEF) (left ventricular ejection fraction [LVEF] $\leq 40\%$) or heart failure with preserved ejection fraction (HFpEF) (LVEF $> 40\%$) groups. Patients who underwent invasive CAG were eligible for the analysis. Patients who were on maintenance renal replacement therapy or who initiated renal replacement therapy before CAG were excluded from the study. Hemodynamically unstable patients who required mechanical hemodynamic or ventilator support were also excluded.

The study protocol was in accordance with the Declaration of Helsinki. It was reviewed and approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB No. B-1503-292-117). The IRB waived the informed consent.

Body weight (BWT): weight optimum, weight excess, weight deficiency

The BWT was measured at least 3 times: at admission (BWT_{ADM}), on the day of CAG (BWT_{CAG}) and at the discharge (BWT_{DIS}). BWT measurement was performed after 8 hours of fasting or longer with the same balance. We assumed that BWT_{DIS} approximated patient's optimal dry weight ("weight optimum"). Therefore, the relative difference between BWT_{CAG} and BWT_{DIS} ($\% \Delta BWT_{CAG} = [BWT_{CAG} - BWT_{DIS}] / BWT_{DIS}$ (%)) were calculated. The value of the calculated BWT difference, either positive or negative, represented the "weight excess" or "weight deficiency."

Outcome definition

CI-AKI was defined as an increase $\geq 25\%$ or ≥ 0.5 mg/dL in serum creatinine at 48 hours after CAG and/or the initiation of dialysis after CAG. Improved CI-AKI was defined as the recovery of creatinine level to $< +25\%$ or $< +0.5$ mg/dL of the baseline level, whereas persistent CI-AKI as non-recovered creatinine level at the time of discharge. Chronic kidney disease (CKD) was defined as glomerular filtration rate ≤ 60 mL/min/1.72 m².

The clinical outcomes included in-hospital death, dialysis, mechanical ventilation, intensive care unit (ICU) admission and use of hemodynamic support device, re-hospitalization and all-cause death at 1-year. All-cause death and re-hospitalization for cardiovascular diseases were recorded at 12-months. The follow-up data were collected by the attending physician and stored in the web-based case report form. The mortality data of patients lost to follow-up were collected from the National Death Records.

Statistical analysis

The patients were categorized into CI-AKI and no-CI-AKI groups. Data were presented as numbers and frequencies for categorical variables and as means $\pm$ standard deviation for continuous variables. For comparison among groups, χ^2 test for categorical variables and unpaired Student's t-test or one-way analysis of variance for continuous variables were applied.

Throughout the study, ΔBWT_{CAG} was treated as a continuous covariate. To crudely evaluate the association between ΔBWT_{CAG} and the risk of CI-AKI, a receiver operating characteristic (ROC) curve analysis was used. The ROC curve revealed 3 distinct zones: in the weight excess zone ($\% \Delta BWT_{CAG} > 2.5\%$) and in the weight deficiency zone ($\% \Delta BWT_{CAG} < -1\%$) the positive and negative deviation of $\% \Delta BWT_{CAG}$ predicted CI-AKI, respectively, while in the weight optimum zone ($\% \Delta BWT_{CAG} -1 \sim 2.5\%$), the change of ΔBWT_{CAG} did not have any discriminatory power. Therefore, we performed a piecewise linear spline approach for $\% \Delta BWT_{CAG}$ to quantify the non-linear relationship in the subsequent analysis.¹⁶⁾ The different association between the risk of CI-AKI and the unit change of ΔBWT_{CAG} in each zone is presented separately in the results section.

To further quantify the association between the risk of CI-AKI and $\% \Delta BWT_{CAG}$, we performed a multivariable regression analysis for binomial outcome. Because CI-AKI was frequently observed (i.e., 25% of the study population), we used the modified Poisson regression with a robust error variance approach to estimate the relative risk (RR).¹⁷⁾¹⁸⁾ For multivariable models, we included the significant factors found in the univariate analysis or clinically meaning factors as covariates.¹⁰⁾ The following models were generated to determine the successive influence of potential confounders on the association between ΔBWT_{CAG} and CI-AKI: 1) unadjusted, 2) adjusted only for age and sex, 3) adjusted for age, sex, CKD, diabetes mellitus, anemia, hypotension, HFrEF or HFpEF, serum level of B-type natriuretic peptides (by tertiles), serum albumin, intra-aortic balloon pump use and contrast dye volume. Kaplan-

Meier estimates and Cox regression analyses were used to compare 3-month and 1-year survival between patients with CI-AKI and no-CI-AKI.

Analyses were performed with STATA version 12 (Stata-Corp LP, College Station, TX, USA) and R programming version 3.1.4 (The R Foundation for Statistical Computing, Vienna, Austria). A 2-sided p value <0.05 was considered statistically significant.

RESULTS

The study population

A total of 2,188 patients with AHF were admitted at the 3 participating centers. Of them, 727 patients underwent CAG. We excluded 35 patients who were on maintenance dialysis and 17 patients who initiated dialysis before CAG. Because the creatinine level in 80 patients and BWT in one patient were not available, 594 patients were included in the final analysis (**Supplementary Figure 1**).

The mean age was 69.9 ± 12.9 years, 40.1% were female, 65.5% had hypertension, 42.3% had diabetes mellitus, and 51.0% had CKD. Fifty-seven percent of the patients had HFrEF, defined as LVEF $\leq 40\%$ and 83% had lung congestion on chest X-ray at admission.

Incidence and risk factors of CI-AKI

Overall, CI-AKI occurred in 147 patients (24.7%). Among patients who had CI-AKI, 104 patients (70.7%) had persistent CI-AKI and 90 patients (61.2%) underwent dialysis after CAG during hospitalization.

Table 1 presents the clinical and procedural characteristics in patients with and without CI-AKI. Patients with CI-AKI had higher prevalence of CKD (68.0% vs. 45.4%, $p < 0.001$), higher N-terminal pro-B-type natriuretic peptide levels (7,786 [interquartile range {IQR}, 2,500–20,313] pg/mL vs. 4,235 [IQR, 1,761–9,298] pg/mL, $p < 0.001$), and lower serum protein levels (6.2 ± 1.1 mg/dL vs. 6.6 ± 0.7 mg/dL; $p = 0.002$) and albumin levels (3.5 ± 0.6 mg/dL vs. 3.8 ± 0.5 mg/dL; $p < 0.001$) than those without CI-AKI. Regarding echocardiographic parameters, patients with CI-AKI had greater E/E' than those without CI-AKI (22 ± 14 vs. 19 ± 11 , $p = 0.04$). The amount of contrast dye was greater in patients with CI-AKI with a marginal statistical significance (146.3 ± 130.6 mL vs. 127.51 ± 112.1 mL, $p = 0.10$). The rate of percutaneous coronary intervention and the prescription of statins did not differ between the 2 groups.

Independent predictors of CI-AKI

Patients with CI-AKI had greater absolute deviation of BWT on CAG day than those without CI-AKI ($|\% \Delta \text{BWT}_{\text{CAG}}|$ 3.2%, range 1.1–8.9% vs. 2.5%, range 0.9–5.1%, $p = 0.003$) (**Figure 1A**). We used the explorative regression model to understand the association of $\Delta \text{BWT}_{\text{CAG}}$ and the risk of CI-AKI. A J-shaped relationship was found between the risk of CI-AKI and $\Delta \text{BWT}_{\text{CAG}}$ (**Figure 1B**): both BWT decrease in the weight deficiency zone and BWT increase in the weight excess zone were associated with increased risk for CI-AKI. This relationship was not present in the weight optimum zone.

In univariable and multivariable models after adjustment for clinically meaningful covariates, $\Delta \text{BWT}_{\text{CAG}}$ was an independent predictor of CI-AKI (**Table 2** and **Supplementary Figure 2**). After full-adjustment, every 1% decrease in BWT in the weight deficiency zone and every

Table 1. Characteristics of patient groups with CI-AKI and no CI-AKI

Variables	No CI-AKI (n=447)	CI-AKI (n=147)	p value
General characteristic			
Age (years)	70.21±12.78	68.84±13.24	0.27
Female	174 (38.9)	64 (43.5)	0.32
Hypertension	287 (64.2)	102 (69.4)	0.25
Diabetes mellitus	181 (40.5)	70 (47.6)	0.13
CKD	203 (45.4)	100 (68.0)	<0.001
Ischemic heart disease	141 (31.5)	46 (31.3)	0.96
New-onset HF	261 (58.4)	92 (62.6)	0.37
HFrEF	257 (57.5)	82 (55.8)	0.72
Lung congestion	368 (82.3)	123 (83.7)	0.71
NYHA functional class			0.24
II	56 (12.5)	12 (8.2)	
III	153 (34.2)	47 (32.0)	
IV	238 (53.2)	88 (59.9)	
Atrial fibrillation	119 (26.6)	35 (23.8)	0.50
Aggravation factors			
ACS/ischemia	214 (47.9)	82 (55.8)	0.10
Tachyarrhythmia	82 (18.3)	17 (11.6)	0.06
Infection	50 (11.2)	8 (5.4)	0.04
Non-compliance	25 (5.6)	10 (6.8)	0.59
Medication			
Intravenous diuretics	334 (74.7)	118 (80.3)	0.17
Intravenous inotropes	209 (46.8)	87 (59.2)	0.009
ACE inhibitor	47 (10.5)	16 (10.9)	0.90
ARB	129 (28.9)	48 (32.7)	0.38
RAS inhibitor	173 (38.7)	62 (42.2)	0.46
Beta-blocker	134 (30.0)	43 (29.3)	0.87
Spironolactone	65 (14.5)	19 (12.9)	0.63
Medication for CI-AKI prophylaxis			
N-Acetylcysteine prophylaxis	103 (23.0)	33 (22.4)	0.88
HMG-CoA inhibitor	164 (36.7)	44 (29.9)	0.14
Physical findings			
Systolic blood pressure (mmHg)	131.45±29.05	131.38±31.37	0.98
Diastolic blood pressure (mmHg)	77.99±18.69	76.37±18.59	0.37
Heart rate (beat per minutes)	93.00±24.98	92.10±24.70	0.71
Body weight on CAG day (kg)	59.83±12.84	60.34±12.42	0.67
Laboratory findings			
Creatinine (μmol/L)	112.3±58.3	198.0±176.8	<0.001
GFR (mL/min/1.73m ²)	66.3±29.6	50.9±52.5	<0.001
Blood urea nitrogen (mmol/L)	9.00±5.09	12.22±6.70	<0.001
NT-proBNP (ng/L)	4,235 (1,761–9,298)	7,786 (2,500–20,313)	<0.001
Troponin I (μg/L)	0.14 (0.04–2.57)	0.30 (0.05–5.88)	0.20
Total protein (g/L)	65.5±7.3	62.4±11.0	0.002
Albumin (g/L)	37.6±4.8	35.2±6.1	<0.001
C-reactive protein (nmol/L)	29.6±50.1	39.0±68.1	0.14
Echocardiographic findings			
LV ejection fraction (%)	35.75±13.53	37.15±12.66	0.37
LV EDV (mL)	143.20±71.24	142.20±68.02	0.90
E wave (m/s)	0.88±0.36	0.93±0.40	0.16
A wave (m/s)	0.77±0.53	0.79±0.28	0.75
E' wave (cm/s)	5.21±2.13	4.80±1.98	0.07
E over E'	19.10±10.81	21.77±14.47	0.04
LA volume index (mL/m ²)	61.43±37.24	71.65±46.33	0.08
Body weights (kg)			
(A) Body weight on admission	60.69±12.93	61.32±12.80	0.61
(B) Body weight on CAG day	59.83±12.84	60.34±12.42	0.67
(C) Body weight on discharge	58.48±12.86	58.74±12.89	0.83

(continued to the next page)

Table 1. (Continued) Characteristics of patient groups with CI-AKI and no CI-AKI

Variables	No CI-AKI (n=447)	CI-AKI (n=147)	p value
Body weight excess from discharge weight (%)			
On admission (A–C)/C	4.05±5.28	5.02±8.58	0.20
Absolute deviation	3.73 (1.69–6.95)	4.13 (1.45–10.40)	0.06
On CAG day (B–C)/C	2.54±4.80	3.26±7.28	0.26
Absolute deviation	2.46 (0.94–5.07)	3.20 (1.13–8.86)	0.003
Procedure			
Percutaneous coronary intervention	168 (37.6)	60 (40.8)	0.49
Contrast dye amount (mL)	127.5±112.1	146.3±130.6	0.10
Days between admission and CAG (days)	2.63±3.4	3.3±5.8	0.17

Values are presented as number (%), number (range) or mean±standard deviation.

ACE = angiotensinogen-converting enzyme; ACS = acute coronary syndrome; ARB = angiotensin II receptor blocker; CAG = coronary angiography; CI-AKI = contrast-induced acute kidney injury; CKD = chronic kidney disease; GFR = glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HMG-CoA = β -hydroxy β -methylglutaryl-CoA; LA = left atrium; LV = left ventricle; LV EDV = left ventricle end-diastolic volume; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; RAS = renin-angiotensin system.

1% increase in BWT in the weight excess zone was associated with 13% (RR, 1.13; 95% confidence interval [CI], 1.07–1.20) and 9% (RR, 1.09; 95% CI, 1.03–1.16) increased risk for CI-AKI, respectively. By contrast, change in $\Delta\text{BWT}_{\text{CAG}}$ in weight optimum zone was not associated with increased risk for CI-AKI (RR, 1.05; 95% CI, 0.91–1.21). Other independent predictors of CI-AKI included previous CKD (RR, 2.08; 95% CI, 1.63–4.71) and the amount of contrast dye (RR, 1.01 for each 10 mL; 95% CI, 1.002–1.022).

Clinical outcomes

Patients with CI-AKI had worse in-hospital outcomes; they had more ICU admission, mechanical ventilation and mechanical hemodynamic support, and higher in-hospital death

Figure 1. Risk of CI-AKI and body weight deviance on CAG day. (A) ROC curve of $\%\Delta\text{BWT}_{\text{CAG}}$ to predict CI-AKI vs. no CI-AKI in whole study group revealed 3 zones of $\Delta\text{BWT}_{\text{CAG}}$ with distinct classifying characteristics (left upper panel). In optimum zone, $\%\Delta\text{BWT}_{\text{CAG}}$ was a poor predictor (AUC, 0.50; p=0.99) (right upper panel). In excess zone (left lower panel) and deficiency zone (right lower panel), $\%\Delta\text{BWT}_{\text{CAG}}$ was a significant predictor with opposite direction (excess zone; AUC, 0.65; p<0.001; deficiency zone; AUC, 0.72; p=0.001). (B) Predicted probability of CI-AKI according to relative body weight deviance from dry weight on CAG ($\%\Delta\text{BWT}_{\text{CAG}}$). The solid black line represents predicted risk. The light-blue area represents 95% confidence interval. There is a J-shaped relationship between the risk of CI-AKI and $\Delta\text{BWT}_{\text{CAG}}$; the risk is lowest when $\Delta\text{BWT}_{\text{CAG}}$ was around 0%.

AUC = area under the curve; BWT = body weight; $\Delta\text{BWT}_{\text{CAG}}$ = deviation of body weight on coronary angiography day; CAG = coronary angiography; CI-AKI = contrast-induced acute kidney injury; ROC = receiver operating characteristic.

Table 2. Independent predictors of CI-AKI

Variables	RR (95% CI)	p value
Model 1 (univariate)		
Body weight status on CAG day ($\Delta\text{BWT}_{\text{CAG}}$)		
Every 1% decrease of weight in deficiency zone ($<-1\%$)	1.11 (1.053–1.168)	<0.001
Every 1% increase of weight in optimum zone ($-1-2.5\%$)	1.00 (0.889–1.134)	0.95
Every 1% increase of weight in excess zone ($>2.5\%$)	1.05 (1.026–1.082)	<0.001
Model 2 ($\Delta\text{BWT}_{\text{CAG}}$ adjusted by age and sex)		
Body weight on CAG day ($\Delta\text{BWT}_{\text{CAG}}$)		
Every 1% decrease of weight in deficiency zone ($<-1\%$)	1.11 (1.053–1.167)	<0.001
Every 1% increase of weight in optimum zone ($-1-2.5\%$)	1.01 (0.890–1.135)	0.94
Every 1% increase of weight in excess zone ($>2.5\%$)	1.05 (1.026–1.080)	<0.001
Age	0.99 (0.982–1.004)	0.20
Sex (female)	1.19 (0.893–1.596)	0.23
Model 3*		
Body weight on CAG day ($\Delta\text{BWT}_{\text{CAG}}$)		
Every 1% decrease of weight in deficiency zone ($<-1\%$)	1.13 (1.065–1.201)	<0.001
Every 1% increase of weight in optimum zone ($-1-2.5\%$)	1.05 (0.909–1.213)	0.51
Every 1% increase of weight in excess zone ($>2.5\%$)	1.09 (1.032–1.162)	0.003
Age >75 years [†]	0.79 (0.559–1.123)	0.19
Sex (female)	0.98 (0.714–1.359)	0.93
CKD [†]	2.08 (1.628–4.710)	<0.001
Diabetes mellitus [†]	1.31 (0.954–1.788)	0.10
Anemia [†]	1.17 (0.826–1.670)	0.37
Hypotension (systolic BP <80 mmHg) [†]	1.33 (0.754–2.344)	0.32
HFrEF	1.02 (0.670–1.562)	0.92
High B-type natriuretic peptide (highest tertile compared to lowest)	1.47 (0.861–2.493)	0.16
Albumin (every 1 mg/dL)	0.75 (0.561–1.014)	0.06
Contrast dye volume (every 10 mL)	1.01 (1.002–1.022)	0.02
IABP use [†]	0.64 (0.369–1.114)	0.12

$\Delta\text{BWT}_{\text{CAG}}$ = deviation of body weight on coronary angiography day; CAG = coronary angiography; CI = confidence interval; CI-AKI = contrast-induced acute kidney injury; CKD = chronic kidney disease; HFrEF = heart failure with reduced ejection fraction; IABP = intra-aortic balloon pump; RR = relative risk.

* $\Delta\text{BWT}_{\text{CAG}}$ adjusted by clinically important covariates and significant covariates from univariable regression;

[†]Denotes predictors reported from previous literature.¹⁰⁾

(16.3% vs. 5.1%, $p<0.001$) than those without CI-AKI (**Table 3**). After adjustment, CI-AKI was associated with 2.5-fold increased risk of in-hospital death (RR, 2.50; 95% CI, 1.45–4.31) (**Supplementary Table 1**).

Regarding the post-discharge outcomes, patients with CI-AKI had higher 3-month and 1-year mortality than those without CI-AKI (3-month: 29.3% vs. 10.5%, $p<0.001$; hazard ratio [HR], 2.82; 95% CI, 1.54–5.14; 1-year: 38.1% vs. 17.4%, $p<0.001$; HR, 2.16; 95% CI, 1.40–3.34). When stratified according to the renal function recovery at hospital discharge, the 1-year

Table 3. In-hospital clinical outcome and CI-AKI

Variables	No CI-AKI (n=447)	CI-AKI (n=147)	p value
Mechanical ventilation	130 (29.1)	60 (40.8)	0.008
Mechanical ventilation day(s)	5.5±9.9	9.2±13.5	0.03
Hemodynamic support device	57 (12.8)	32 (21.8)	0.008
ICU admission	232 (51.9)	95 (64.6)	0.007
ICU admission day(s)	6.6±6.5	10.1±14.0	0.02
Hospitalization day(s)	14.7±13.6	23.9±36.4	0.003
In-hospital death	23 (5.1)	24 (16.3)	<0.001
1-year all-cause death	78 (17.4)	56 (38.1)	<0.001
1-year rehospitalization	199 (46.9)	63 (51.2)	0.40

Values are presented as number (%) or mean±standard deviation.

CI-AKI = contrast-induced acute kidney injury; ICU = intensive care unit.

Figure 2. Clinical outcome. (A) CI-AKI and clinical outcomes: Patients CI-AKI had higher all-cause mortality than those without CI-AKI. In addition, there was no difference in mortality between patients with persistent and those with improved CI-AKI. (B) Body weight on CAG day and outcomes: patients with weight excess and weight deficiency on the CAG day had higher all-cause mortality compared to those with weight optimum. CAG = coronary angiography; CI = confidence interval; CI-AKI = contrast-induced acute kidney injury; CV = cardiovascular; HR = hazard ratio.

mortality did not differ between patients with persistent and improved CI-AKI (**Figure 2A**). Patients with CI-AKI had higher 1-year rehospitalization with a marginal significance.

The timing of CAG and the volume status on CAG day

The timing of CAG varied among the patients. Overall, 29.5%, 24.4%, 10.3%, 9.3%, 5.7%, and 21% of the patients underwent CAG on the day of admission, on the hospital day 1, 2, 3, 4, and 5 or later, respectively. When we plotted $\Delta\text{BWT}_{\text{CAG}}$ by CAG day, the proportion of patients undergoing CAG in weight optimum zone was significantly larger when CAG was performed on hospital day 1 or later (**Supplementary Figure 3**). Interestingly, patients who underwent CAG on day 1 or 2 had 46% (odds ratio [OR], 0.56; 95% CI, 0.36–0.85) and 52% (OR, 0.48; 95% CI, 0.251–0.91) reduced risk of CI-AKI compared to those who underwent CAG on admission day, respectively. In addition, patients with weight excess and deficiency had increased mortality than those in weight optimum (**Figure 2B**).

Subgroup analysis

Figure 3 presents the summarized result of predefined subgroups. CKD did not exert significant impact on $\Delta\text{BWT}_{\text{CAG}}$ and CI-AKI risk. Half of the study patients (296 patients, 50%) presented with acute coronary syndrome (ACS) and they were more likely to have diabetes mellitus and de novo heart failure (**Supplementary Table 2**). Overall the relationship between $\Delta\text{BWT}_{\text{CAG}}$ and CI-AKI risk was similar in patients with and without ACS (**Supplementary Figures 4 and 5 and Supplementary Table 3**).

DISCUSSION

In this study, we showed that the incidence of CI-AKI was 24.7% in patient with AHF undergoing CAG, and they had worse in-hospital and long-term outcomes. Furthermore, a J-shaped relationship was found between $\Delta\text{BWT}_{\text{CAG}}$ and CI-AKI. The lowest risk for CI-AKI was observed in patients in the weight optimum zone, whose BWT was closer to their

Figure 3. Subgroup analysis. The forest plot depicts the association of % Δ BWT_{CAG} and the risk of CI-AKI in each subgroup. Δ BWT_{CAG} = deviation of body weight on coronary angiography day; CI = confidence interval; CI-AKI = contrast-induced acute kidney injury; CKD = chronic kidney disease; GFR = glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; OR = odds ratio.

discharge weight (**Figure 4**). To the best of our knowledge, our study is the first to report the incidence, risk factors and clinical outcomes of CI-AKI in patients with AHF undergoing CAG.

Previous studies in the general population reports that the incidence of CI-AKI after CAG ranges from 2% to 25% and that underlying HF is associated with 2-fold increased risk of CI-AKI.⁹⁾¹⁰⁾ In this study, we showed that the incidence of CAG-induced CI-AKI in AHF patients was strikingly high and that the majority of AHF with CI-AKI had persistent renal dysfunction.¹⁰⁾¹⁹⁾ The hemodynamic instability, neuro-endocrine stimulation, decongestion therapy with diuretics, exposure to contrast media, and coronary manipulation during CAG may all contribute to the significantly poor renal outcomes.¹¹⁾²⁰⁾ Most importantly, patients with CI-AKI more than doubled the risk for in-hospital and 1-year mortality. It is unknown whether CI-AKI is a marker for high-burden of comorbidities or a mediator for progression of cardiovascular disease.⁹⁾²¹⁻²³⁾ However, because many patients with AHF have hemodynamic instability and are vulnerable to stressful stimuli, CI-AKI may initiate or accelerate the

Figure 4. Optimal timing for CAG to prevent CI-AKI. Renal perfusion pressure is determined by mean arterial pressure and central venous pressure. The probability for CI-AKI is lowest when the patients achieve their body weight optimum on the day of CAG, i.e., euvolemic state. $\Delta\text{BWT}_{\text{CAG}}$ = deviation of body weight on coronary angiography day; CAG, coronary angiography; CI-AKI = contrast-induced acute kidney injury; CVP = central venous pressure.

progression of the cardiorenal syndrome: the vicious feedback cycle between the failing heart and kidney may result in poor clinical outcomes.¹¹⁾

There was a J-shaped relationship between BWT on CAG day and risk of CI-AKI. Although BWT is not the exact measure for volume status, it can be used as a rough surrogate. A typical patient with acute decompensation has a volume overload with weight gain over several days or weeks. With effective decongestion, the patient loses weight and reaches dry weight at discharge. We cautiously presumed that weight excess, optimum, and deficiency may roughly correspond to hyper-, eu-, and hypovolemic state, respectively.

Renal perfusion is determined by the difference between mean arterial and renal venous pressure. Currently, supplying 25–30 mL/kg of isotonic saline is the most validated prophylactic measure for CI-AKI. This strategy aims to increase urinary flow to prevent CI-AKI. However, previous randomized trials that studied this measure excluded patients with pulmonary edema or AHF.²¹⁾²²⁾²⁴⁻²⁶⁾ Furthermore, most patients with AHF have systemic congestion, as 83% of our patients had lung congestion at admission. Therefore, hydration strategy may even worsen systemic congestion and the renal perfusion with activation of renin-angiotensin-aldosterone system (RAAS) resulting in contrast media retention and increased risk of CI-AKI.¹¹⁾ In line with the pathophysiology, in the weight excess zone, every 1% increase of BWT was associated with 13% increased risk for CI-AKI.

By contrast, hypovolemia triggers physiological mechanisms of volume preservation via activation of RAAS and vasopressin. Arterial underfilling or low effective circulating volume may lead to contrast media retention via neurohormonal activation,²⁷⁾ which can be reversed with volume replacement. In this study weight deficiency was associated with increased risk of CI-AKI.

Currently, no consensus statements exist regarding the most appropriate timing to detect coronary artery disease in patients with AHF patients. However, because ischemia is the leading acute etiology for AHF, the latest HF practice guideline recommends immediate identification and treatment of ACS (C of “CHAMP” acronym).⁵⁾ Our study confirmed the J-curve relationship with a “sweet spot” of minimal CI-AKI risk. The J-shaped relationship may reflect the time required to restore volume status and optimize hemodynamics in patients with AHF. It may also reflect reduction in neuro-endocrine stimulation.

Patients with weight optimum had better 1-year survival than those with weight excess or deficiency on CAG day. Therefore, it is reasonable to perform CAG after dry weight achievement, unless the patient has compelling indication for immediate CAG, i.e., ST-elevation myocardial infarction, cardiogenic shock, refractory angina or other sign of ongoing myocardial damage or hemodynamic instability.⁴⁾⁶⁾ If the patients' dry weight is unknown, postponing CAG until the hospital day 2 may be reasonable, because the risk of CI-AKI was the lowest on day 2.

There are several limitations. This is a post hoc analysis of a prospective cohort study. Although the cohort was large, it was not a randomized trial, and therefore confounding factors could have influenced the outcomes. The timing of CAG during hospitalization may represent patient subgroups with different pathophysiology and clinical outcome. We did not capture the reason for the initiation of dialysis after CAG. Some patients may have undergone dialysis for AKI aggravation after CAG whereas others may have undergone dialysis to prevent AKI. We attempted to mitigate this effect through vigorous risk adjustment in a multivariable model but cannot preclude the possibility of non-measured confounding factors. Therefore, the result does not provide a causal relationship. The findings in this study are hypothesis-generating, rather than definitive. Further studies should assess whether initial decongestion before CAG might improve renal perfusion and the urine flow and reduce the risk of CI-AKI.

In conclusion, in patients hospitalized for AHF who undergo CAG, CI-AKI is common and associated with worse clinical outcomes. Achieving dry weight before CAG may reduce the risk of CI-AKI.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Univariable and multivariable regression model for in-hospital mortality

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Supplementary Table 2

Characteristics of patients with and without ACS

[Click here to view](#)

Supplementary Table 3

Body weight deviation and CI-AKI in patients with and without ACS

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Supplementary Figure 1

Study flow diagram.

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Supplementary Figure 2

Adjusted risk of CI-AKI and body weight deviance on CAG day. Predicted probability of CI-AKI according to relative body weight deviance from discharge weight on CAG ($\% \Delta \text{BWT}$ on CAG). Adjusted for age, sex, CKD, diabetes, anemia, hypotension, HFrEF vs. HFpEF, IABP use, B-type natriuretic peptide, serum albumin and contrast dye amount. The solid black line represents predicted risk. The gray area represents 95% confidence interval.

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Supplementary Figure 3

Risk of CI-AKI and timing of CAG and outcome according to weight. Risk of CI-AKI and timing of CAG: Predicted probability of CI-AKI according to timing of CAG. Upper: the solid black line represents predicted risk of CI-AKI. The gray area represents 95% confidence interval. Lower: density plot depicting the distribution of timing of CAG.

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Supplementary Figure 4

Interaction between body weight deviance on CAG day and other independent predictors. The graphs represent the interaction between $\% \Delta \text{BWT}_{\text{CAG}}$ and independent risk factors (A) CKD, (B) serum albumin level, (C) contrast dye volume, and (D) HFrEF vs. HFpEF to predict the risk of CI-AKI from the final multivariable model.

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Supplementary Figure 5

Body weight deviance on CAG day and risk of CI-AKI in patients with and without ACS. Predicted probability of CI-AKI according to relative body weight deviance from dry weight on CAG ($\% \Delta \text{BWT}$ on CAG). Univariate model in patient group presenting with (A) ACS or (B) no-ACS. The solid black line represents predicted risk. The gray area represents 95% confidence interval.

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