Submitted: 31 March, 2023 Accepted: 19 May, 2023 Published: 08 November, 2023 DOI:10.22514/sv.2023.112

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ORIGINAL RESEARCH

The effect of early diuretics administration on acute kidney injury progression after cardiac surgery: a *post-hoc* analysis of a multicenter retrospective cohort study (BROTHER study)

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Abstract

Positive fluid balance is associated with acute kidney injury (AKI) following cardiac surgery in a dose-dependent manner. Although diuresis is a common intervention for fluid overload, the optimal timing of diuretic administration for preventing AKI after cardiac surgery remains unclear. We aimed to investigate whether early administration of diuretics after cardiac surgery is associated with subsequent AKI progression. This was a *post-hoc* analysis of a multicenter retrospective cohort study that included adult patients admitted to 14 intensive care units (ICUs) after elective cardiac surgery between January and December 2018. The exposure variable was the administration of intravenous diuretics during the initial 24 hours after ICU admission. The primary outcome was AKI progression, defined as one or more AKI stages using Kidney Disease: Improving Global Outcomes creatinine and urine output criteria between 24 and 72 hours compared with the worst stage during the first 24 hours. We used multivariable logistic regression analyses to assess the association between early administration of diuretics and AKI progression. Among the 718 patients analyzed, 335 (47%) received intravenous diuretics within the first 24 hours, and AKI progression occurred in 115 patients (16%). In the multivariable analyses, early diuresis was not associated with AKI progression (odds ratio, 1.12; 95% confidence interval, 0.74–1.69), confirmed by sensitivity analyses. Early administration of intravenous diuretics was not associated with a lower risk of AKI progression after cardiac surgery.

Keywords

Acute kidney injury; Diuretics; Fluid overload; Cardiac surgery; Kidney replacement therapy; Intensive care

1. Introduction

Acute kidney injury (AKI), a frequent postoperative complication in cardiac surgery patients, has been correlated with increased rates of mortality, morbidity, and extended periods of hospitalization and intensive care unit (ICU) stay [1–3]. Even with modern improvements in diagnostic and treatment modalities, the development of a solid strategy for preventing or treating cardiac surgery-associated AKI (CSA-AKI) remains elusive [4].

ICU patients receive considerable amounts of fluid for resuscitation, medication, and nutrition. Given that fluid therapy is a fundamental approach to counteract intraoperative hypotension during cardiac surgeries, patients who undergo these procedures commonly experience fluid overload [5]. There is evidence linking fluid overload to an increased risk of mortality, AKI, and the need for kidney replacement therapy (KRT) in patients undergoing cardiac surgery [6, 7]. The use of diuretics is a prevalent strategy to manage fluid accumulation, with the anticipation that their early use of diuretics could prevent AKI progression. However, the evidence from small, randomized trials examining the effect of early diuretic administration on kidney outcomes has been inconclusive in cardiac surgery patients [8, 9]. Therefore, the most beneficial timing of diuretics administration remains uncertain [10].

With these uncertainties in mind, this study was designed to test a hypothesis that the administration of diuretics during the first 24 hours would reduce AKI progression between 24 and 72 hours among postoperative cardiac surgery patients based on the data of a multicenter retrospective cohort study.

2. Materials and methods

This was a *post-hoc* analysis of a multicentric retrospective cohort study that included adult patients who had undergone cardiac surgery in 14 ICUs in Japan (BROTHER study; UMIN-

CTR; trial ID: UMIN000037074). The primary aim of the BROTHER study was to investigate the effects of relative hypotension on AKI progression in adults undergoing elective cardiac surgery. The details of the BROTHER study have been reported previously [11]. We complied with the Strengthening the reporting of observational studies in epidemiology (STROBE) guidelines (see **Supplementary Table 1** for completed checklist).

2.1 Participants and data sources/measurement

We consecutively studied patients aged 18 years or older admitted to the ICU after planned coronary artery bypass grafting (CABG) or valve surgery between 01 January and 31 December 2018. The exclusion criteria were: (i) patients who were discharged from the ICU within 24 hours; (ii) patients who underwent emergency cardiac surgery; (iii) patients on mechanical circulatory support (*i.e.*, extracorporeal membrane oxygenation, intra-aortic balloon pumping, or ventricular assist device) during the first 24 hours after ICU admission; (iv) patients with postoperative blood pressure (BP) recordings at an interval of longer than 1 hour; (v) patients without available BP readings within 365 days before the surgery; (vi) patients who opted out of this study; and (vii) patients censored for data collection. Consistent with the Declaration of Helsinki and ethical guidelines for epidemiological research by Japan's Ministry of Education, Culture, Sports, Science, and Technology and Ministry of Health, Labour and Welfare, we published the eligibility criteria and how to refuse participation in this study using a poster in each participating hospital or on their website. As soon as a patient or their family member informs investigators about their refusal to participate, we exclude the patient. No patient opted out of this study. We collected the data from November 2019 and November 2020. However, 42 patients had to be censored for data collection as the COVID-19 pandemic hindered data collection for this study.

The collection of demographic data, comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE) II score [12], and Sequential Organ Failure Assessment score [13] was carried out. Information on surgical procedures, as well as the use of vasopressors, inotropes, and diuretics within the initial 24 hours after ICU admission were also gathered.

In the initial 24-hour period following ICU admission, we collected data on central venous pressure (CVP), which were taken hourly. For our analysis, we calculated the average CVP over each four-hour span. If, within any given four-hour window, a CVP reading was unavailable, we imputed the closest available measurement to that specific time frame.

2.2 Exposure and outcome variables

The primary exposure variable was the early use of diuretics, defined as administering intravenous diuretics (loop diuretics, mineralocorticoid receptor antagonists, acetazolamide, and human atrial natriuretic peptide) within the first 24 hours after ICU admission. We classified the cohort into two groups: those who received early administration of diuretics (the early diuretics group) and those who did not (the non-early diuretics group).

The primary outcome variable was AKI progression. We determined AKI progression through a three-step process:

(1) The worst AKI stage was first identified during the first 24 hours following ICU admission.

(2) Subsequently, the worst AKI stage was determined within the time frame between 24 and 72 hours after ICU admission.

(3) The two AKI stages identified in the aforementioned steps were then compared.

AKI progression was defined as an elevation of at least one AKI stage within the latter time frame (between 24 and 72 hours), as compared to the former (during the first 24 hours). **Supplementary Fig. 1** presents the framework of this study design. Our assessments were based on the creatinine and urine output criteria of Kidney Disease: Improving Global Outcomes guidelines [14].

In each hospital involved in the study, the intensivist responsible for data collection clinically determined the baseline serum creatinine level before surgery based on the patient's medical records. The secondary outcome variables comprised major adverse kidney event (MAKE) within 30 days after the surgery, in-hospital mortality, the requirement for KRT during ICU stay, fluid balance on the second and third day of ICU admission, duration of ICU stay, length of hospital stay, duration of mechanical ventilation, new-onset atrial fibrillation during ICU stay, and stroke during the hospital stay. We defined MAKE30 as a composite outcome of death, new initiation of KRT, or doubling of serum creatinine from the preoperative level within 30 days after the surgery [15]. We censored fluid balance at the time of ICU discharge due to potential inaccuracies in data collection post-ICU discharge.

2.3 Statistical analysis

Among the patients meeting the eligibility criteria, we excluded from our analysis patients with end-stage kidney disease or those whose preoperative serum creatinine exceeded 3.5 mg/dL. We also excluded those without urine output data, those diagnosed with stage 3 AKI, those on norepinephrine dose or epinephrine >0.2 μg/kg/min, patients with hypernatremia (>150 mEq/L), and the patients undergoing, based on the data within the initial 24 hours after ICU admission. In case of any missing data, except for CVP, the number of missing data was noted, and the analysis was conducted excluding these cases. The methodology for imputing postoperative CVP values is described in the Participants and data source/measurement section (**Supplementary Table 2**).

We reported categorical variables as numbers (percentages) and continuous variables as medians with interquartile ranges. A comparison of baseline characteristics and hemodynamic parameters between patients who did and did not receive early diuretic administration was made using the chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. We evaluated the impact of early diuretic use on AKI progression using multivariable logistic regression analyses adjusted for age, APACHE II score, average CVP values during the first 24 hours after ICU admission, chronic hypertension, preoperative left ventricular

ejection fraction, preoperative CVP levels, baseline serum creatinine, cardiopulmonary bypass (CPB), intraoperative fluid balance, and surgery time. We selected these variables based on their clinical relevance and importance as risk factors for AKI in previous studies [11, 16–21]. We also performed multivariable analyses for the secondary outcomes using the same set of covariates.

For the primary outcome, we carried out the following sensitivity analyses, including: (1) the inclusion of only patients with intraoperative fluid balance >5% of the body weight due to its association with AKI progression in cardiac surgery patients [6], (2) the inclusion of only patients receiving any vasopressor or inotrope during the first 24 hours after ICU admission considering the association between shock and AKI [22], (3) the exclusion of patients who received human natriuretic atrial peptide during the first 24 hours because it may worsen renal function after cardiac surgery [23], (4) the exclusion of patients who underwent off-pump CABG, and (5) the exclusion of centers with at least one censoring occurred during the study period.

In addition, as part of our exploratory analyses, we compared the temporal changes of the worst AKI stage between groups: (1) between early diuretics and non-early diuretics groups and (2) between patients with and without AKI progression.

All analyses were performed using Stata version 16 (StataCorp, College Station, TX, USA), R studio software version 2023.03.0+386 (R Foundation for Statistical Computing, Vienna, Austria), and EZR (Saitama Medical Center, Jichi Medical University, ver. 1.36), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). We considered a two-sided p value < 0.05 as statistically significant.

3. Results

Among 1568 adult patients admitted to the ICUs after cardiac surgery between January and December 2018, 870 patients were registered in the BROTHER study. After excluding 152 patients, 718 patients were eligible for this *post-hoc* analysis (Fig. 1). No patients were lost to follow-up.

Table 1 describes preoperative patient characteristics and perioperative management. Intravenous diuretics were administered in 335 patients (47%) received intravenous diuretics during the first 24 hours after ICU admission. The median age was 71 years, and most patients had chronic hypertension. A higher proportion of patients undergoing mitral valve surgery and longer surgery time and cardiopulmonary bypass time were observed in the early diuretics group. Among the vasopressors and inotropes administered in the first 24 hours, dobutamine was the most common agent. Vasoconstrictors (*i.e.*, norepinephrine, dopamine, vasopressin and phenylephrine) were more frequently used in the early diuretics group. Further data on preoperative patient characteristics and perioperative management are described in **Supplementary Table 3**.

Table 2 summarizes the type of diuretic agents used during the first 24 hours. Loop diuretics were the most common agents, followed by human atrial natriuretic peptide. More than one types of diuretic agent were used in 67 patients (20%).

Table 3 summarizes the clinical outcomes. The primary outcome, AKI progression, occurred in 115 patients (16%). **Supplementary Tables 4 and 5** present the changes in AKI stages based on the exposure variable and primary outcome measure, respectively. In patients with AKI progression, the urine output criteria identified worsening AKI stage more frequently than the serum creatinine criteria (**Supplementary Table 6**). **Supplementary Fig. 2** presents the temporal trend of serum creatinine levels. No statistically significant difference was observed between the two groups at any time point. The fluid balance in the early diuretics group was smaller on the second day of the ICU stay but greater on the third day (Table 3). Patients in the early diuretics group, discontinued mechanical ventilation earlier than those in the non-early diuretic group; however, the duration of hospitalization was prolonged (Table 3).

Multivariable logistic regression analyses (Table 4) found that the adjusted odds ratio of early diuretic use for AKI progression was 1.12 (95% confidence interval (CI), 0.74–1.69; $p = 0.61$). The sensitivity analyses found similar results with the primary analysis. The multivariable analyses conducted for the secondary outcomes revealed that the early administration of diuretics was associated with a reduction in fluid balance on the second day of ICU stay. However, it was also associated with an increase in fluid balance on the third day and a prolonged hospital stay (**Supplementary Table 7**).

4. Discussion

4.1 Key findings

This *post-hoc* analysis of a multicenter retrospective cohort study investigated whether early administration of diuretic agents was associated with a decreased risk of subsequent AKI progression in adult patients after elective cardiac surgery. Among 718 patients eligible for this analysis, 47% received early diuretic agents, and 16% experienced AKI progression. The multivariable logistic regression analysis found that early diuretic use was not associated with AKI progression, which was also confirmed by sensitivity analyses.

4.2 Relationship with previous studies

Fluid therapy is one of the crucial parts of routine intensive care practice; however, a positive fluid balance is frequently observed after fluid resuscitation, which is associated with detrimental clinical outcomes, including mortality and worsening kidney function among critically ill patients [24–26]. Active fluid removal using diuretic agents and ultrafiltration is the cornerstone for the treatment for fluid accumulation. However, the most appropriate timing to start diuretics and ultrafiltration remains an open question [10]. Our findings are consistent with those of a recent meta-analysis of randomized controlled trials which evaluated the relationship between furosemide and AKI in patients undergoing cardiac surgery [27]. This meta-analysis found no effect of furosemide on the incidence of AKI or the requirement of KRT.

The biggest challenge in fluid management is that both fluid depletion and overload can exacerbate kidney function. Thus, diuretics are effective in patients with fluid overload while

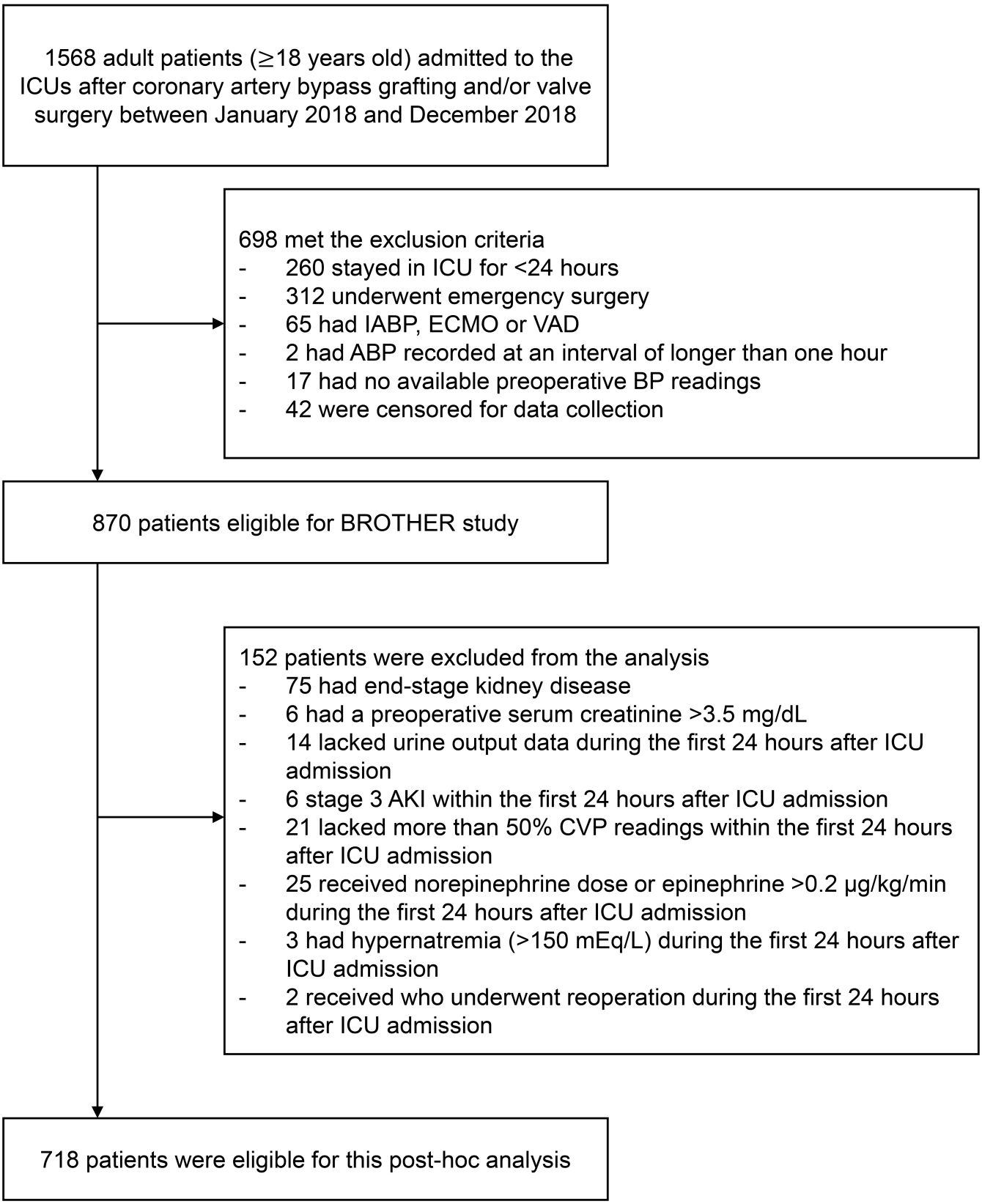

FIGURE 1. Patient flow chart. ICU: intensive care unit; IABP: intra-aortic balloon pumping; ECMO: extracorporeal membrane oxygenation; VAD: ventricular assist device; ABP: arterial blood pressure; BP: blood pressure; AKI: acute kidney injury; CVP: central venous pressure.

TABLE 1. Patient characteristics and perioperative management.

	All N = 718	Early diuretics N = 335	Non-early diuretics N = 383	*p* value
Age, yr	71 (63–77)	71 (65–77)	70 (62–76)	0.40
Males, n (%)	446 (62)	206 (61)	240 (63)	0.81
Chronic hypertension, n (%)	527 (73)	237 (71)	290 (76)	0.16
Chronic kidney disease, n (%)	297 (41)	139 (41)	158 (41)	1.00
Previous cardiac surgery, n (%)	70 (10)	31 (9.3)	39 (10)	0.77
LVEF, n (%)				
>50%	582 (81)	267 (80)	315 (82)	0.84
35%–50%	109 (15)	54 (16)	55 (14)	
20%–34%	25 (3.5)	13 (3.9)	12 (3.1)	
<20%	2 (0.3)	1 (0.3)	1 (0.3)	
Baseline serum creatinine, mg/dL	0.85 (0.70–1.03)	0.83 (0.70–1.02)	0.85 (0.70–1.03)	0.67
Preoperative CVP, mmHg	3 (3–6)	3 (3–6)	3 (3–6)	0.81
Type of surgery, n (%)				
CABG	245 (34)	105 (31)	140 (37)	0.16
Mitral valve	235 (33)	123 (37)	112 (29)	0.04
Aortic valve	349 (49)	156 (47)	193 (50)	0.33
Tricuspid valve	127 (18)	57 (20)	60 (17)	0.66
Pulmonary valve	9 (1.3)	4 (1.2)	5 (1.3)	1.00
Surgery time, minutes	341 (276–427)	351 (284–446)	335 (271–407)	<0.001
Cardiopulmonary bypass, n (%)	625 (87)	300 (90)	325 (85)	0.08
Cardiopulmonary bypass time, minutes[a]	176 (135–231)	180 (137–235)	173 (134–225)	0.18
Intraoperative fluid balance, mL	2250 (1192–3317)	2184 (1027–3332)	2300 (1393–3302)	0.26
APACHE II score	13 (11–15)	13 (11–15)	12 (10–15)	0.35
Vasopressors and inotropes within the first 24 hours after ICU admission				
Norepinephrine, n (%)	269 (37)	149 (44)	120 (31)	<0.001
Maximal dose[b], µg/kg/min	0.07 (0.04–0.11)	0.08 (0.05–0.12)	0.06 (0.04–0.10)	0.21
Epinephrine, n (%)	4 (0.6)	1 (0.4)	3 (0.8)	0.71
Maximal dose[b], µg/kg/min	0.06 (0.04–0.07)	0.05 (0.05–0.05)	0.07 (0.05–0.08)	1.00
Dopamine, n (%)	122 (17)	78 (23)	44 (11)	<0.001
Maximal dose[b], µg/kg/min	3.0 (1.9–4.1)	2.8 (1.8–4.2)	3.4 (2.0–4.1)	0.37
Vasopressin, n (%)	25 (3.5)	20 (6.0)	5 (1.3)	<0.001
Phenylephrine, n (%)	9 (1.3)	8 (2.4)	1 (0.3)	0.03
Dobutamine, n (%)	385 (54)	182 (54)	203 (53)	0.78
Maximal dose[b], µg/kg/min	2.5 (1.6–3.4)	2.7 (1.8–3.5)	2.5 (1.6–3.4)	0.58
PDE inhibitors, n (%)	122 (17)	74 (22)	48 (13)	<0.001
CVP within the first 24 hours after ICU admission, mmHg	8.3 (6.6–10.4)	8.4 (6.9–10.3)	8.4 (6.9–10.3)	0.36
Worst AKI stage within the first 24 hours after ICU admission, n (%)				
No AKI	502 (70)	232 (69)	270 (70)	0.66
AKI stage 1	182 (25)	89 (27)	93 (24)	
AKI stage 2	34 (4.7)	14 (4.2)	20 (5.2)	

APACHE: acute physiology and chronic health evaluation; CABG: coronary artery bypass grafting; CVP: central venous pressure; ICU: intensive care unit; LVEF: left ventricular ejection fraction; PDE: phosphodiesterase; AKI: acute kidney injury.

[a]*: The denominator was patients whose surgery was conducted with cardiopulmonary bypass.*

[b]*: The denominator was patients to whom each vasoactive agent was given during the first 24 hours after ICU admission.*

TABLE 2. Use of diuretics during the first 24 hours after ICU admission.

Administered diuretics	N (%)
Total	335
Loop	157 (47)
Human atrial natriuretic peptide	109 (33)
Mineralocorticoid receptor antagonists	2 (0.6)
Loop and human atrial natriuretic peptide	28 (8.4)
Loop and mineralocorticoid receptor antagonists	21 (6.3)
Loop, mineralocorticoid receptor antagonists, and human atrial natriuretic peptide	16 (4.8)
Mineralocorticoid receptor antagonists and human atrial natriuretic peptide	2 (0.6)

TABLE 3. Clinical outcomes.

	All N = 718	Early diuretics N = 335	Non-early diuretics N = 383	*p* value
AKI progression, n (%)	115 (16)	57 (17)	58 (15)	0.56
MAKE30, n (%)	6 (0.8)	4 (1.2)	2 (0.5)	0.43
Hospital mortality, n (%)	3 (0.4)	2 (0.6)	1 (0.3)	0.60
Need for KRT during ICU stay, n (%)	4 (0.6)	2 (0.6)	2 (0.5)	1.00
Fluid balance on the second day of ICU stay, mL	532 (−100–1272)	482 (−191–1139)	599 (−22–1366)	0.04
Fluid balance on the third day of ICU stay[a], mL	−419 (−1234–104)	−282 (−845–136)	−588 (−1427–27)	<0.001
Length of ICU stay, day	3 (2–4)	3 (2–4)	3 (2–4)	0.60
Length of hospital stay, day	20 (15–27)	21 (17–29)	19 (14–26)	<0.001
Length of mechanical ventilation in ICU, (h)	8 (5–17)	7 (4–16)	10 (5–17)	<0.001
New-onset atrial fibrillation during ICU stay[b], n (%)	85 (15)	33 (13)	52 (17)	0.21
Stroke during hospital stay, n (%)	12 (1.7)	8 (2.4)	4 (1.0)	0.24

AKI: acute kidney injury; KRT: kidney replacement therapy; MAKE: major adverse kidney event; ICU: intensive care unit.
[a]: The denominator was patients who stayed in the ICU over three calendar days or more (N = 706 for the overall population, N = 329 for early diuretics, and N = 377 for non-early diuretics).
[b]: The denominator was patients without a history of atrial fibrillation before ICU admission (N = 557 for the overall population, N = 254 for early diuretics, and N = 303 for non-early diuretics).

TABLE 4. The effects of early diuresis on acute kidney injury progression in multivariable analyses.

	OR (95% CI)	*p* value
Overall population	1.12 (0.74–1.69)	0.61
Sensitivity analyses		
Patients with intraoperative fluid overload[a]	1.21 (0.57–2.57)	0.62
Patients receiving any vasopressor or inotrope within the first 24 hours after intensive care unit admission	1.20 (0.74–1.95)	0.46
Excluding patients receiving human atrial natriuretic peptide	0.66 (0.37–1.19)	0.17
Excluding patients who underwent off-pump CABG	1.19 (0.76–1.87)	0.44
Excluding centers with at least one censored case during the study period	1.10 (0.72–1.67)	0.66

Abbreviations: CI: confidence interval; OR: odds ratio; CABG: coronary artery bypass grafting.
[a]: Fluid overload was defined as intraoperative fluid balance >5% of the body weight.

deleterious in patients with hypovolemia. In addition, the lack of a highly reliable method to assess fluid status complicates the appropriate administration of diuretic agents. Of note, we found that early diuresis was associated with accelerated fluid removal on the following day of surgery. Taken together, we could hypothesize that the benefits of early diuretics administration in patients with volume overload were canceled by its harms in patients with normal or even hypovolemic fluid status. In line with our findings, a recent randomized trial in critically ill patients found less fluid accumulation in patients assigned to the restrictive fluid administration and active fluid removal strategy than in patients assigned to usual care and no difference in kidney outcomes [28].

It is also worth noting that the type of diuretic agents could impact clinically relevant outcomes. Since loop diuretics are the leading diuretic agent in intensive care settings, efforts should be made to avoid their common adverse effects. One major side effect is hypokalemia, an independent risk factor for perioperative arrhythmia in patients undergoing cardiac surgery [29]. Co-administration of mineralocorticoid receptor antagonists may prevent or at least alleviate hypokalemia. Another adverse effect is metabolic alkalosis, which is often accompanied by respiratory acidosis and may inhibit the weaning from mechanical ventilation or increase mortality in critically ill patients [30]. Acetazolamide, a carbonic anhydrase inhibitor, can attenuate metabolic alkalosis and stimulate respiratory drive. In addition, a recent randomized trial demonstrated that the addition of acetazolamide to loop diuretic therapy, compared with loop diuretics plus placebo, led to more successful decongestion in patients with acute decompensated heart failure [31]. In our study, none of the patients were given acetazolamide, and 20 patients (7.2% among the early diuretics group) received mineralocorticoid receptor antagonists within the first 24 hours, which was consistent with a previous report [32]. The use of combination diuretic therapy may result in successful fluid removal without causing electrolyte or acid-base disorders, thus improving outcomes.

The adverse effects of the early diuretics administration on fluid balance and hospitalization should be interpreted with caution, as the analyses presented here are exploratory by definition. The fluid balance measured on the third day of ICU admission may not reflect the actual fluid balance accurately, as the fluid balance measurements were censored at ICU discharge and the median ICU stay was only three days. In particular, patients with a stable postoperative course may have been discharged from the ICU within a short period on the third day. Moreover, the potentially negative effect on the hospital stay was not consistently observed across all outcomes. Therefore, these findings should require careful assessment.

4.3 Significance and implications

This study does not support the routine use of early diuretic agents after cardiac surgery. We found that early diuretic therapy resulted in less fluid accumulation without a reduced incidence of AKI progression. Since diuretic agents may temporarily increase urine output even in patients with hypovolemia, it is vital to evaluate the patient's volume status before the administration of diuretic agents. With no definitive parameter or biomarker to predict the successful administration of diuretic agents, clinicians should consider a variety of elements, including physical symptoms, hemodynamic metrics, laboratory data, and radiological/sonographic signs [10].

Future research should address identifying the optimal timing to start diuretics using multimodality approaches. In addition, future trials are warranted to assess the effect of a combination of diuretics with different mechanisms after cardiac surgery.

4.4 Strengths and limitations

Our study has several limitations. First, we did not collect data on intravenous diuretics during cardiac surgery or oral diuretics after the surgery. However, we took into account several intraoperative confounders (*e.g.*, intraoperative fluid balance) in the multivariable analyses to adjust the effects of intraoperative management on postoperative AKI progression. In addition, diuretics are typically administered intravenously immediately after cardiac surgery. Second, a higher proportion of patients in the early diuretics group were observed to receive vasopressors and inotropes during the first 24 hours after ICU admission, compared to patients without early diuresis. However, a sensitivity analysis in patients receiving vasopressors or inotropes confirmed the primary analysis. Third, inherent to any observational cohort study, we could not control unmeasured or unknown confounders that could have influenced the findings. These might include specific details of cardiopulmonary bypass (CPB) settings, or the underlying indications for diuretic administration. Variations in intraoperative management or clinical conditions could have potentially influenced our results.

5. Conclusions

We found that early use of diuretic agents was not associated with a reduced risk of AKI progression after cardiac surgery. Our findings do not support the routine use of early administration of diuretics to prevent the worsening of AKI.

ABBREVIATIONS

AKI: acute kidney injury; APACHE: Acute Physiology and Chronic Health Evaluation; BROTHER: Blood pressure and Relative Optimal Target after Heart surgery in Epidemiologic Registry; CABG: coronary artery bypass grafting; CI: confidence interval; CPB: cardiopulmonary bypass; CVP: central venous pressure; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; KRT: kidney replacement therapy; MAKE: major adverse kidney event; OR: odds ratio.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

YK—had full access to all the data in the study and took responsibility for the integrity of the data; Drafting of the manuscript. YK and TY—Study concept and design; Acquisition of data; Analysis and interpretation of data. All authors gave a critical appraisal of the manuscript and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The ethics committee of Kameda Medical Center approved this study (No. 19-013), and all the ethics committees of participating hospitals approved an opt-out method of informed consent. Since this is a retrospective cohort study, we applied the opt-out method of informed consent for participation.

ACKNOWLEDGMENT

We would like to thank all the colleagues in the BROTHER study participating hospitals who performed the extensive data entry.

The BROTHER study group: Kameda Medical Center: Yuki Kotani; Jikei University School of Medicine: Takahiro Koga; Okinawa Chubu Hospital: Izumi Nakayama; Tottori University Faculty of Medicine: Masato Nakasone; Wakayama Medical University: Mami Shibata; Hokkaido University Hospital: Tomonao Yoshida; Kobe City Medical Center General Hospital: Akihisa Taguchi, Daisuke Kawakami; Hirosaki University Graduate School of Medicine: Noriko Mikami, Junichi Saito, Mirei Kubota, Tsubasa Oyama; Kurashiki Central Hospital: Jun Kamei; Yokohama City Minato Red Cross Hospital: Isao Nagata, Shinsuke Karatsu; Tokyo Bay Urayasu Ichikawa Medical Center: Naoki Yamaguchi; Yokohama City University Hospital: Takayuki Kariya; Iwate Prefectural Central Hospital: Hiroshi Nashiki; Hiroshima Citizens Hospital: Koji Kido, Hiroki Omiya.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Yuki Kotani is serving as one of the Editorial Board members of this journal. We declare that Yuki Kotani had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to KPV.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1722151267791192064/attachment/Supplementary%20material.docx.

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How to cite this article: Yuki Kotani, Takuo Yoshida; on behalf of the BROTHER study group. The effect of early diuretics administration on acute kidney injury progression after cardiac surgery: a *post-hoc* analysis of a multicenter retrospective cohort study (BROTHER study). Signa Vitae. 2023; 19(6): 175-183. doi: 10.22514/sv.2023.112.