



Prognostic Impact of Loop Diuretics in Patients With Chronic Heart Failure

– Effects of Addition of Renin-Angiotensin-Aldosterone System Inhibitors and β -Blockers –

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Background: It remains to be elucidated whether addition of renin-angiotensin-aldosterone system (RAAS) inhibitors and/or β -blockers to loop diuretics has a beneficial prognostic impact on chronic heart failure (CHF) patients.

Methods and Results: From the Chronic Heart failure Analysis and Registry in the Tohoku district 2 (CHART-2) Study (n=10,219), we enrolled 4,134 consecutive patients with symptomatic stage C/D CHF (mean age, 69.3 years, 67.7% male). We constructed Cox models for composite of death, myocardial infarction, stroke and HF admission. On multivariate inverse probability of treatment weighted (IPTW) Cox modeling, loop diuretics use was associated with worse prognosis with hazard ratio (HR) 1.28 (P<0.001). Furthermore, on IPTW multivariate Cox modeling for multiple treatments, both low-dose (<40 mg/day) and high-dose (\geq 40 mg/day) loop diuretics were associated with worse prognosis with HR 1.32 and 1.56, respectively (both P<0.001). Triple blockade with RAS inhibitor(s), mineral corticoid (aldosterone) receptor antagonist(s) (MRA), and β -blocker(s) was significantly associated with better prognosis in those on low-dose but not on high-dose loop diuretics.

Conclusions: Chronic use of loop diuretics is significantly associated with worse prognosis in CHF patients in a dose-dependent manner, whereas the triple combination of RAAS inhibitor(s), MRA, and β -blocker(s) is associated with better prognosis when combined with low-dose loop diuretics. (*Circ J* 2016; **80**: 1396–1403)

Key Words: Chronic heart failure; Loop diuretics; Prognosis; Treatment

Loop diuretics play a central role in the relieving of congestive symptoms by promoting renal secretion of sodium in patients with acute decompensated heart failure (HF) and by maintaining water balance in patients with chronic HF (CHF).^{1,2} The current guidelines recommend the use of loop diuretics as a class I indication to improve symptoms in both HF patients with reduced ejection fraction (HFrEF) and in those with HF with preserved ejection fraction (HFpEF).^{1,3} Loop diuretics, however, are known to activate the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), which could accelerate HF progression.^{4,5} Loop diuretics could also cause worsening renal func-

tion and electrolyte disturbance.⁶ Several studies, which were mainly designed for HFrEF patients, reported that loop diuretic use was associated with increased morbidity and mortality.^{7–11} It is also true, however, that there is no alternative medication to loop diuretics to effectively relieve congestive symptoms and that it is difficult to perform a randomized clinical trial from an ethical point of view. Thus, investigation of the use of loop diuretics in the management of HF was carried out using an observational cohort study. Given that loop diuretics activate the RAAS and SNS, it is logical to speculate that the addition of β -blockers and RAAS inhibitors, including angiotensin-converting enzyme inhibitors (ACEI), angiotensin

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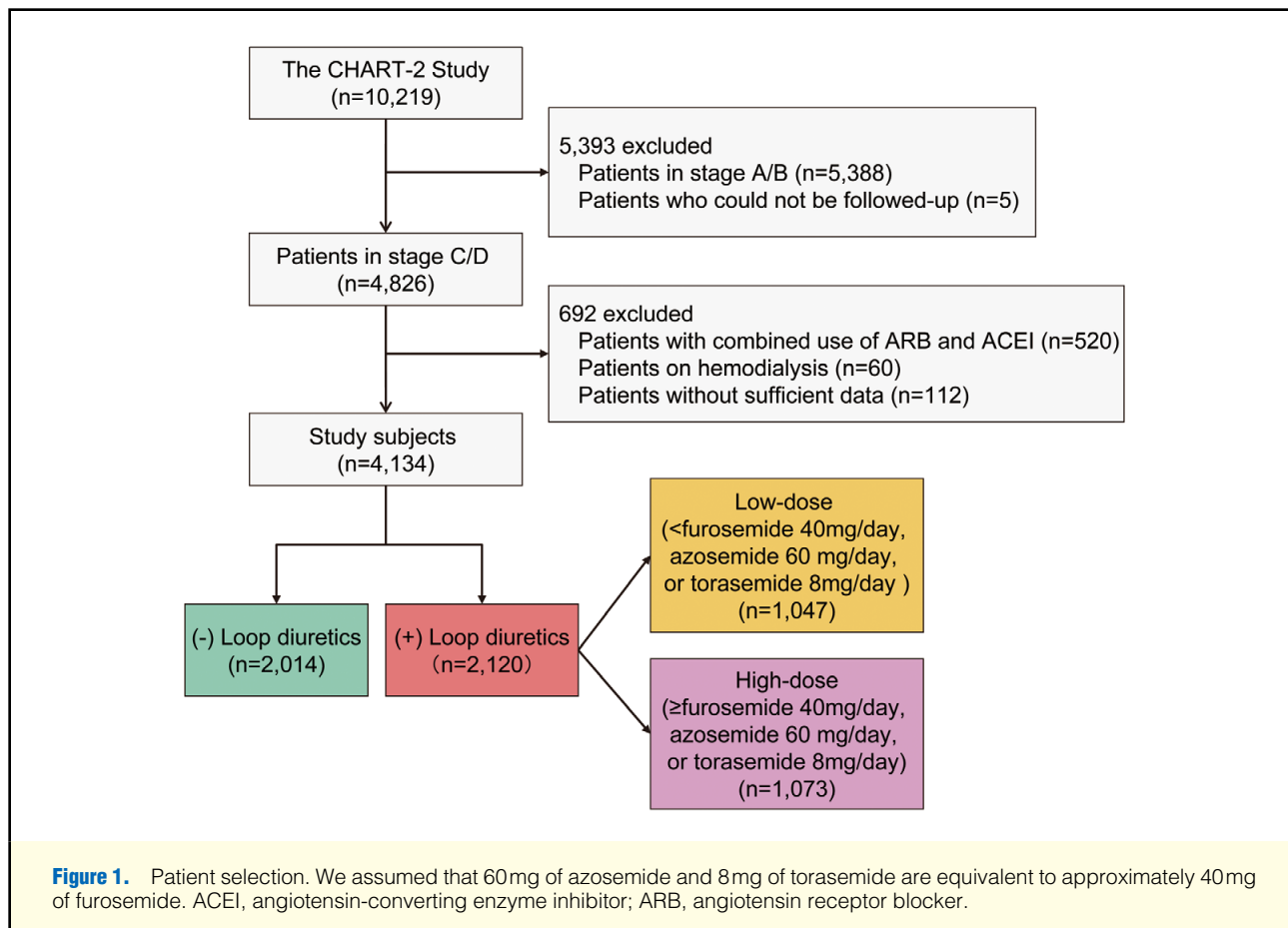
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receptor blockers (ARB) and mineral corticoid (aldosterone) receptor antagonists (MRA), could be beneficial for CHF patients.

Recent epidemiological studies have demonstrated the trend of increased prevalence of HFpEF worldwide.¹²⁻¹⁴ Furthermore, although evidence-based therapy has been implemented in real-world practice,¹³ no therapeutic strategy has yet been established for HFpEF patients.^{1,3} Thus, it is important to clarify the prognostic impact of loop diuretics in symptomatic HF. Moreover, no studies have previously addressed the impact of the addition of RAAS inhibitors and β -blockers to loop diuretics in HF patients. In the present study, we thus examined the prognostic impact of loop diuretics with a special reference to the addition of RAAS inhibitors and/or β -blockers in the treatment of CHF patients in the Chronic Heart failure Analysis and Registry in the Tohoku district 2 (CHART-2) Study.^{13,15-17}

Methods

Subjects and Inclusion Criteria

The details of the design, objectives and baseline characteristics of the CHART-2 Study have been described previously (NCT00418041).^{13,15-17} Briefly, the CHART-2 Study was started in October 2006 and successfully enrolled by the end of March 2010 10,219 consecutive patients with stage B/C/D HF according to the ACCF/AHA guidelines¹ or those with coronary artery disease in stage A. The protocol of the CHART-2 Study was approved by the local ethics committee in the 24 participating

hospitals and written informed consent was obtained from all patients. HF was diagnosed by experienced cardiologists using the criteria of the Framingham Heart Study.¹⁸ All data and events have been and will be surveyed at least once per year until the end of March 2018. We enrolled 4,826 consecutive patients with symptomatic stage C/D CHF in the present study. Among them, 60 patients on hemodialysis, 520 with combination use of ACEI and ARB at enrollment and 112 with insufficient data were excluded. Finally, we included 4,134 patients with stage C/D CHF in the present study (Figure 1).

Data Collection and Loop Diuretics Dose

Detailed data on baseline characteristics, including medication and loop diuretics dose, were recorded at the time of enrollment. In the present study, 1,559 patients (73.5%) used furosemide, while 265 (12.5%) and 187 (8.8%) used azosemide and torasemide, respectively. Another 109 patients (5.1%) used dual or triple combination of loop diuretics. Given that most of the patients used furosemide, we assumed that all patients used furosemide in the present study. We assumed that 60 mg azosemide is equivalent to approximately 40 mg furosemide¹⁹ and 8 mg torasemide to approximately 40 mg furosemide, considering the smaller body mass index (BMI) of Japanese patients compared with the previous Western study.²⁰

Outcomes

The primary outcome of the present study was a composite endpoint of all-cause death, HF admission, acute myocardial infarction and stroke. Mode of death was determined by the

Table 1. Baseline Patient Characteristics vs. Use of Loop Diuretics			
Loop diuretics	(-) (n=2,014)	(+) (n=2,120)	P-value
Age (years)	68.2±12.2	70.5±12.5	<0.001
Female	569 (28.3)	765 (36.1)	<0.001
History of admission for HF	719 (35.7)	1,472 (69.4)	<0.001
Etiology			
IHD	1,210 (60.1)	851 (40.1)	<0.001
DCM	141 (7.0)	390 (18.4)	<0.001
HCM	74 (3.7)	52 (2.5)	0.02
Hypertensive heart disease	106 (5.3)	111 (5.2)	1.00
Valvular heart disease	124 (6.1)	276 (13.0)	<0.001
Comorbidities			
Hypertension	1,752 (87.0)	1,781 (84.0)	<0.001
Hyperuricemia	782 (38.8)	1,404 (66.2)	<0.001
Diabetes	730 (36.2)	819 (38.6)	0.12
Atrial fibrillation	583 (29.0)	1,031 (48.7)	<0.001
CVD	388 (19.3)	432 (20.4)	0.39
Anemia	597 (29.7)	819 (38.6)	<0.001
Clinical status			
NYHA class III/IV (%)	161 (8.0)	304 (14.4)	<0.001
BMI (kg/m ²)	24.1±3.6	23.4±4.0	<0.001
SBP (mmHg)	129±18	123±20	<0.001
DBP (mmHg)	74±12	70±12	<0.001
Heart rate (beats/min)	71±14	73±15	<0.001
Laboratory data			
LVEF (%)	60.6±13.6	53.7±16.0	<0.001
LVDd (mm)	46.7±14.8	51.8±13.8	<0.001
BUN (mg/dl)	17.4±6.7	22.1±11.4	<0.001
Serum sodium (mEq/L)	141±2.8	140±2.9	<0.001
Serum potassium (mEq/L)	4.4±0.4	4.4±0.5	0.06
eGFR (ml/min/1.73 m ²)	65.4±19.3	56.8±21.3	<0.001
BNP (pg/ml)	69.1 (27.2–162.2)	143.2 (62.9–310.0)	<0.001
Medications			
ACEI	770 (38.2)	960 (45.3)	<0.001
ARB	680 (33.8)	740 (34.9)	0.45
β-blockers	1,143 (56.8)	1,024 (48.3)	<0.001
MRA	170 (8.4)	839 (39.6)	<0.001
Thiazide	75 (3.7)	63 (3.0)	0.19
Digitalis	267 (13.3)	710 (33.5)	<0.001
Statin	875 (43.4)	689 (32.5)	<0.001

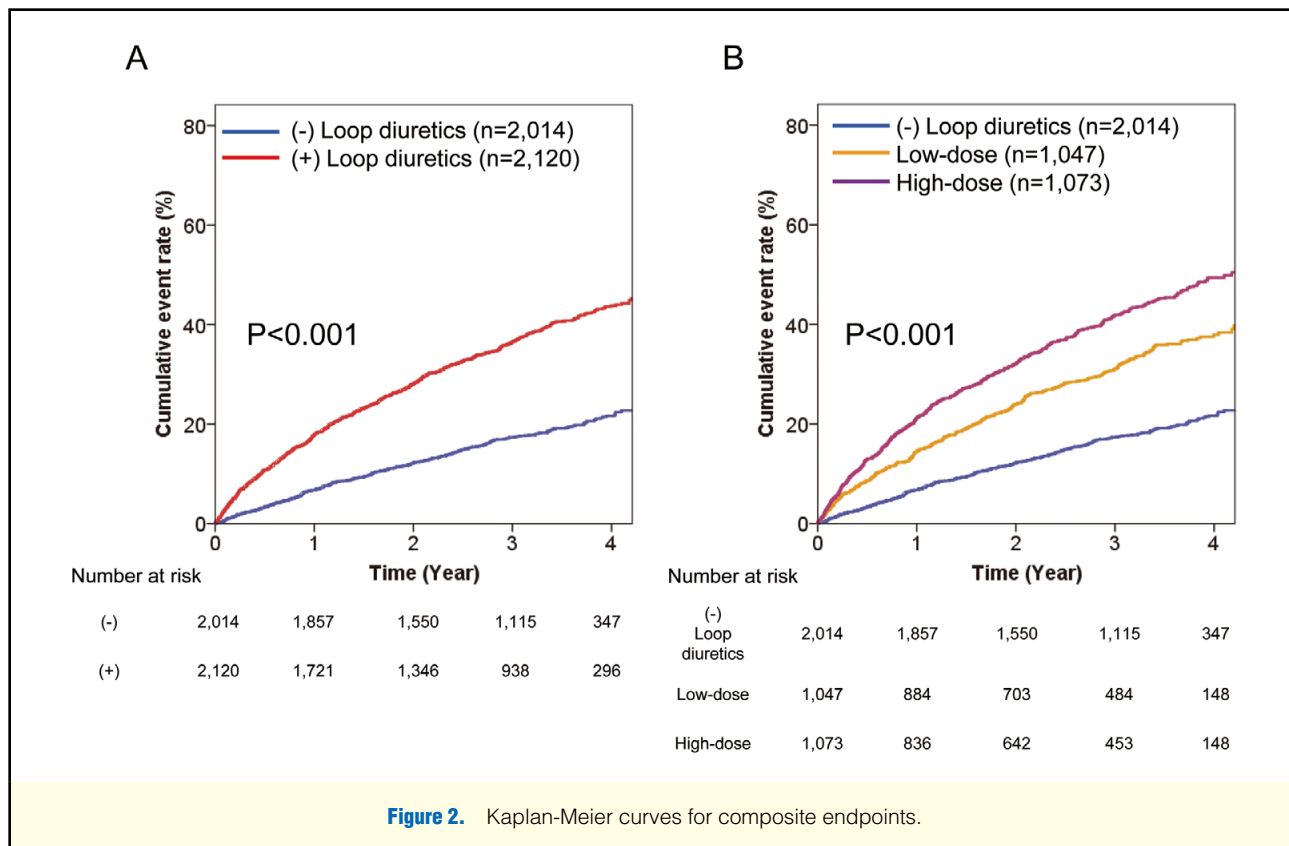
Data given as mean±SD, n (%) or median (IQR). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HF, heart failure; IHD, ischemic heart disease; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineral corticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure.

attending physician(s) at each hospital and was confirmed by one independent physician who was a member of the Tohoku Heart Failure Association.¹⁵

Statistical Analysis

First, we compared the baseline characteristics and the prognosis between patients with loop diuretics and those without it. Descriptive statistics, including mean±SD, frequency (percentage) for continuous and categorical data, are given according to loop diuretic treatment category. Brain natriuretic peptide (BNP) is described as median (IQR) due to skewed distribution. Group comparisons were done using Welch's t-test for

continuous variables and Fisher's exact test for categorical variables. Survival curves were estimated using the Kaplan-Meier procedure and compared with two-sided log-rank test. To reduce confounding effects related to differences in background between patients with and without loop diuretics, propensity score (PS) methods were used in combination with Cox regression modeling. For calculation of PS, we used a logistic regression model in which the treatment status of loop diuretics was regressed for the following 31 baseline characteristics: age, male sex, systolic and diastolic blood pressure (SBP and DBP), heart rate, BMI, New York Heart Association (NYHA) class, history of hospitalization for HF, hypertension,



diabetes mellitus, hyperuricemia, atrial fibrillation, ventricular tachycardia, stroke, cancer, ischemic etiology, anemia, BNP, serum sodium, serum potassium, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVDd), ACEI or ARB, β -blocker, MRA, thiazide, statin, and digitalis. Area under the curve for PS for loop diuretics use was 0.83 (95% confidence interval [CI]: 0.82–0.85). To reduce confounding in the time-to-event observational data, the inverse probability of treatment weighted (IPTW) method was used.^{16,21}

Second, we examined the prognostic impact of loop diuretics according to dose. Given that the median furosemide dose was 40mg in the present study, we divided the patients on loop diuretics into a low-dose (<40mg/day, n=1,047) and a high-dose (\geq 40mg/day, n=1,073; **Figure 1**) group. To reduce confounding effects related to differences in patient background among those without loop diuretics and those with low-dose or high-dose diuretics, PS methods were used in combination with Cox regression modeling. PS for multiple treatments was estimated using generalized boosted models with the 31 variables described above.²² Then, to reduce confounding in the time-to-event observational data, the IPTW method was used.

Third, we examined the prognostic impact of addition of RAAS inhibitors including MRA and β -blockers to loop diuretics treatment in patients on low-dose and high-dose loop diuretics. Single use of RAAS inhibitors including MRA or β -blockers was defined as single blockade, combination use of RAAS inhibitors or β -blockers as double blockade, and triple combination use of RAAS inhibitors and β -blockers as triple blockade. We excluded the patients who used both ACEI and

ARB at enrollment. Stepwise variable selection for Cox proportional hazard model was performed using 27 baseline characteristics: age, male sex, SBP and DBP, heart rate, BMI, NYHA class, history of hospitalization for HF, hypertension, diabetes mellitus, hyperuricemia, atrial fibrillation, ventricular tachycardia, stroke, cancer, ischemic etiology, anemia, BNP, serum sodium, serum potassium, BUN, eGFR, LVEF, LVDd, thiazide, statin, and digitalis. We also performed subgroup analysis stratified by eGFR (<60 or \geq 60ml/min/1.73 m²) and LVEF (<50 or \geq 50%). Covariates for adjustment were selected using backward elimination for stepwise variable selection from the 27 covariates in each stratum of eGFR or LVEF. Then, we constructed Cox hazard models and calculated P-value for interaction using all the selected variables from each stratum of eGFR or LVEF. eGFR was calculated using the modified modification of diet in renal disease equation with the Japanese coefficient²³ at the time of enrollment.

All statistical analysis was performed using IBM SPSS Statistics 21.0 (IBM, Somers, NY, USA) and R 3.2.3 (R Foundation for Statistical Computing, Vienna; <http://www.R-project.org/>). PS analysis for multiple treatments was conducted using the R TWANG package.²² Statistical significance was defined as 2-sided P<0.05.

Results

Baseline Characteristics

Table 1 lists the baseline characteristics of the CHF patients. Mean age was 69.3 years and male patients accounted for 67.7%. The prevalence of ischemic heart disease was 49.4% and mean LVEF was 57.0 \pm 15.3%. Patients with loop diuretics, as compared with those without it, were older and had a

Table 2. Cox Hazard Models for Composite Endpoints

		HR	95% CI	P-value
(-) Loop diuretics	Reference	1.00		
(+) Loop diuretics	Crude	2.44	2.16–2.76	<0.001
	IPTW adjustment	1.28	1.17–1.39	<0.001
(-) Loop diuretics	Reference	1.00		
Low dose	Crude	2.02	1.75–2.34	<0.001
High dose	Crude	2.88	2.51–3.31	<0.001
(-) Loop diuretics	Reference	1.00		
Low dose	IPTW adjustment for multiple treatments	1.32	1.21–1.45	<0.001
High dose	IPTW adjustment for multiple treatments	1.56	1.43–1.71	<0.001

CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighted.

higher proportion of women, non-ischemic heart disease, history of HF at admission and hyperuricemia. Furthermore, they were characterized by higher NYHA class and BUN and lower blood pressure, eGFR and serum sodium in a dose-dependent manner (Tables 1, S1). ACEI and MRA were more often prescribed, while β -blockers were not in those with loop diuretics. Digitalis and MRA were more often prescribed in patients on high-dose loop diuretics (Table S1).

Prognostic Impact of Chronic Loop Diuretics Use

During a median follow-up period of 2.99 years, the composite endpoints occurred in 1,176 patients (28.4%). The patients with loop diuretics, as compared with those without it, had significantly poorer prognosis even after IPTW adjustment (crude hazard ratio [HR], 2.44; 95% CI: 2.16–2.76, $P<0.001$; adjusted HR, 1.28 95% CI: 1.17–1.39, $P<0.001$; Figure 2; Table 2). Furthermore, on IPTW Cox regression hazard modeling for multiple treatments, loop diuretics use was significantly associated with poor prognosis in a dose-dependent manner (low-dose: crude HR, 2.02; 95% CI: 1.75–2.34, $P<0.001$; adjusted HR, 1.32; 95% CI: 1.21–1.45, $P<0.001$; high-dose: crude HR, 2.88; 95% CI: 2.51–3.31, $P<0.001$; adjusted HR, 1.56; 95% CI: 1.43–1.71; $P<0.001$; Figure 2; Table 2).

Combination of RAAS Inhibitors and β -Blockers With Loop Diuretics

We further examined the prognostic impact of loop diuretics with regard to the addition of RAS inhibitors (ACEI or ARB), MRA and β -blockers. In patients on low-dose loop diuretics, multivariate Cox regression hazard modeling showed improved prognosis with adjusted HR for single, double and triple blockade of 0.86 (95% CI: 0.56–1.32, $P=0.20$), 0.77 (95% CI: 0.50–1.19, $P=0.48$) and 0.53 (95% CI: 0.32–0.88, $P=0.04$), respectively (P for trend=0.01; Figure 3A). In contrast, in patients on high-dose loop diuretics, multivariate Cox regression hazard modeling showed no improvement of mortality, with adjusted HR in single, double and triple blockade of 1.33 (95% CI: 0.89–2.01, $P=0.17$), 0.98 (95% CI: 0.65–1.48, $P=0.93$) and 1.04 (95% CI: 0.67–1.61, $P=0.87$), respectively (P for trend=0.26; Figure 3A).

We further performed subgroup analysis with reference to eGFR and LVEF. In the patients with low-dose loop diuretics and eGFR <60 ml/min/1.73 m², as compared with those with no blockers, triple blockade with ACEI, MRA and β -blocker was significantly associated with improved mortality with HR 0.53 (95% CI: 0.32–0.88, $P=0.03$), whereas single or double blockade was not (Figure 3B). In contrast, in the patients with low-dose loop diuretics and eGFR ≥ 60 ml/min/1.73 m², as

compared with those with no blockers, there was only a trend for improved prognosis with RAAS inhibitors and β -blockers (Figure 3B). In the patients with high-dose loop diuretics and eGFR <60 ml/min/1.73 m², there was no improvement of mortality regardless of RAAS inhibitor or β -blockers use (Figure 3C). In contrast, in those with high-dose loop diuretics and eGFR ≥ 60 ml/min/1.73 m², double blockade and triple blockade tended to be associated with improved mortality (P -value for interaction vs. eGFR <60 ml/min/1.73 m² of double blockade and triple blockade, 0.007 and 0.05, respectively; Figure 3C).

In the patients with LVEF $<50\%$, as compared with those with no blockers, there was a significant trend for improved prognosis with RAAS and SNS blockade regardless of loop diuretics dose (P -value for trend for low dose and high dose was <0.001 and 0.01, respectively; Figures 3D,E). In contrast, in the patients with LVEF $\geq 50\%$, there was no improvement of mortality regardless of loop diuretics dose (Figure 3E).

Discussion

The novel findings of the present study are that chronic loop diuretics use in CHF patients was significantly associated with poor prognosis in a dose-dependent manner, whereas addition of RAAS inhibitors and β -blockers was associated with better prognosis, especially when low-dose loop diuretics were used in patients with reduced eGFR or LVEF. These findings underline the clinical importance of the routine combination use of loop diuretics plus RAAS inhibitors and β -blockers in the management of CHF patients.

Loop Diuretic Furosemide and Long-Term Prognosis

In the present study, patients with loop diuretics, as compared with those without it, were characterized by non-ischemic etiology, severe HF status, low blood pressure and renal dysfunction, and chronic use of loop diuretics was significantly associated with worse prognosis in a dose-dependent manner even after adjustment of baseline characteristics. Although similar findings were reported in the subgroup analysis in the previous clinical HF trials,^{7–11} the present study has confirmed them for the first time in a large cohort study with a large number of HFpEF patients. The adverse prognostic effects of furosemide use in HF patients may be mediated by several mechanisms. First, furosemide activates the RAAS and SNS and thus could accelerate further HF progression.^{4,5} Second, furosemide causes renal dysfunction and electrolytes disturbance.^{6,11} Third, furosemide accelerates LV dysfunction and cardiac fibrosis, elevates serum aldosterone and alters calcium

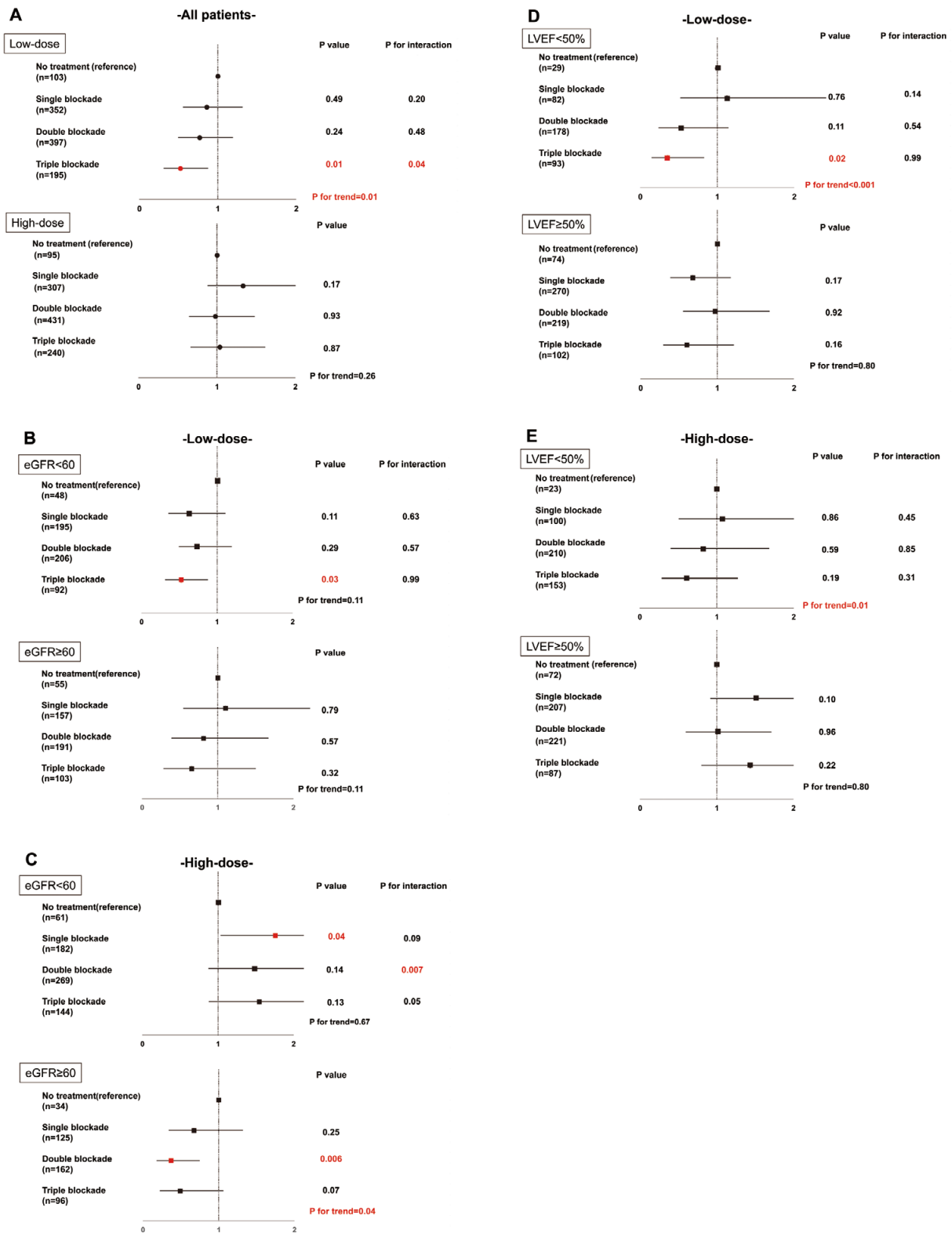


Figure 3. Cox hazard models for composite endpoints. Single blockade, single use of RAS inhibitor, MRA or β -blocker. Double blockade, dual combination use of RAS inhibitor, MRA or β -blocker. Triple blockade, use of all 3 blockers. (A) All patients. (B) Patients on low-dose loop diuretics stratified by estimated glomerular filtration rate (eGFR). (C) Patients on high-dose loop diuretics stratified by eGFR. (D) Patients on low-dose loop diuretics stratified by left ventricular ejection fraction (LVEF). (E) Patients on high-dose loop diuretics stratified by LVEF.

handling.^{24,25} Despite these potential adverse prognostic effects of furosemide, there is no alternative option other than loop diuretics to effectively improve congestive symptoms in severe HF. Indeed, the guidelines recommend the use of loop diuretics to improve congestive symptoms in both HF_{rEF} and HF_{pEF} patients.^{1,3} Thus, appropriate use of loop diuretics is crucial for the improved management of CHF. Considering the activation of the RAAS and SNS by furosemide, combination use of RAAS inhibitors including MRA and β -blockers with furosemide should be an important strategy in CHF practice.

Combination of RAAS Inhibitors and/or β -Blockers With Loop Diuretics

The present results suggest that multiple blockades of RAAS and SNS are beneficial only in HF patients with low-dose loop diuretics. Furosemide activates the RAAS and SNS,^{4,5} accelerates LV dysfunction and elevates serum aldosterone.²⁴ In contrast, partial RAAS blockade could activate one or more RAAS components with resultant activation of angiotensin or aldosterone receptor, which is known as breakthrough phenomenon.²⁶ Thus, combination use of RAAS inhibitors and β -blockers with loop diuretics is important to improve prognosis in HF patients with low-dose loop diuretics. In contrast, in the present study, multiple blockades of RAAS and SNS did not improve mortality in HF patients with high-dose loop diuretics, especially in those with reduced eGFR. Given that reduced eGFR is an important factor of poor response to furosemide,²⁷ high dose is often needed in those patients. High-dose furosemide, however, could further activate the RAAS and SNS, leading to worse prognosis and renal dysfunction. Thus, RAAS inhibitors and β -blockers could exert cardiorenal protective effects in HF patients. In contrast, the RAAS is essential to preserve renal function and glomerular filtration.²⁸ Renal perfusion pressure is a major determinant of glomerular hydraulic filtration pressure.²⁹ The kidney responds to a decrease in blood supply by increasing renin and angiotensin in order to maintain function and glomerular filtration within the normal range, which is known as nephrocentric reaction.²⁹ In CHF patients, renal perfusion is usually decreased along with reduction in cardiac output, followed by activation of the RAAS to maintain renal function. Thus, high-dose loop diuretics and excessive blockade of the RAAS and SNS could result in a vicious cycle of cardiorenal interaction in CHF patients with reduced GFR.

In the present study, combination of RAAS inhibitors and/or β -blockers with loop diuretics did not improve mortality in HF_{pEF} patients. Given that the extent of the involvement of neurohumoral activation in HF progression is smaller in HF_{pEF} than in HF_{rEF},³⁰ the beneficial effects of RAAS inhibitors and β -blockers may be small in HF_{pEF} patients. Furthermore, given that HF_{pEF} patients are usually older than HF_{rEF} patients, renal function could be overestimated in the formula of eGFR.²³ Given that excessive blockade of the RAAS could accelerate renal dysfunction, chronic use of high-dose loop diuretics should be avoided in HF_{pEF} patients.

Potential Benefit of Other Loop Diuretics and Tolvaptan

In the present study, 1,559 patients (73.5%) used furosemide, while 265 (12.5%) and 187 (8.8%) used azosemide and torasemide, respectively. These 2 loop diuretics have different pharmacological properties from furosemide. Azosemide, a long-acting loop diuretic, has been reported to cause no SNS activation in a rat model of HF³¹ and to improve mortality in HF patients compared with furosemide.¹⁹ Torasemide, another

long-acting loop diuretic, has been reported to have similar effects to MRA.³² Thus, it is conceivable that the extent of the RAAS and SNS activation may be smaller in patients on azosemide or torasemide compared with those on furosemide.

In the present study, HF patients with high-dose loop diuretics and reduced eGFR had significantly poor prognosis regardless of the combination use of RAAS inhibitors and β -blockers. Given that RAAS inhibitor dose is usually low due to renal dysfunction in those patients, the beneficial effects of RAAS inhibitors may be limited. Recently, a vasopressin V2 receptor antagonist, tolvaptan, has been used in the management of HF. Tolvaptan binds anti-diuretic hormone receptors in the collecting duct, thereby promoting aquaresis.³³ Furthermore, it has no effect on renal blood flow or RAAS.³⁴ Several studies reported on the effectiveness of the combined use of tolvaptan and furosemide in HF patients with renal dysfunction.^{35,36} Thus, tolvaptan may have beneficial effects in HF patients with reduced eGFR who need high-dose loop diuretics.

Study Limitations

Several limitations should be mentioned for the present study. First, in the present study, the data at enrollment were analyzed, and the possible changes in HF treatment during follow-up were not taken into consideration. Second, more than 500 patients used azosemide and torasemide, and were not excluded from analysis, in order to maintain statistical power. The beneficial effects of long-acting loop diuretics remain to be further examined in future studies. Third, we did not take into consideration the dose of RAAS inhibitors or β -blockers. Finally, given that the CHART-2 Study is an observational study, there might be unmeasured confounding factors that could influence the present results.

Conclusions

The chronic use of loop diuretics is significantly associated with worse prognosis in CHF patients in a dose-dependent manner, whereas the combination of RAAS inhibitors and β -blockers with furosemide is associated with better prognosis when combined with low-dose loop diuretics.

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Conflicts of Interest

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Supplementary Files

Supplementary File 1

Table S1. Baseline patient characteristics vs. loop diuretic dose

CHART-2 Study Organization

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