ORIGINAL

Benefits of guideline-directed medical therapy to loop diuretics in management of heart failure

Kenya Kusunose, MD, PhD[1], Yuichiro Okushi, MD[1], Yoshihiro Okayama, M.Eng.[2], Robert Zheng, MD[1], Michikazu Nakai, PhD[3], Yoko Sumita[3], Takayuki Ise MD, PhD[1], Koji Yamaguchi MD, PhD[1], Shusuke Yagi MD, PhD[1], Hirotsugu Yamada, MD, PhD[4], Takeshi Soeki MD, PhD[1], Tetsuzo Wakatsuki MD, PhD[1], and Masataka Sata, MD, PhD[1]

[1]Department of Cardiovascular Medicine, Tokushima University Hospital, Tokushima, Japan, [2]Clinical Research Center for Developmental Therapeutics, Tokushima University Hospital, Tokushima, Japan, [3]Center for Cerebral and Cardiovascular Disease Information, National Cerebral and Cardiovascular Center, Osaka, Japan, [4]Department of Community Medicine for Cardiology, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan

Abstract : Background : We sought to compare the outcomes of patients receiving combination therapy of diuretics and neurohormonal blockers, with a matched cohort with monotherapy of loop diuretics, using real-world big data. Methods : This study was based on the Diagnosis Procedure Combination database in the Japanese Registry of All Cardiac and Vascular Datasets (JROAD-DPC). After exclusion criteria, we identified 78,685 patients who were first hospitalized with heart failure (HF) between April 2015 and March 2017. Propensity score (PS) was estimated with logistic regression model, with neurohormonal blockers (angiotensin-converting enzyme inhibitor : ACEi or angiotensin receptor blocker : ARB, β-blockers and mineralocorticoid receptor antagonists : MRA) as the dependent variable and 24 clinically relevant covariates to compare the in-hospital mortality between monotherapy of loop diuretics and combination therapies. Results : On PS-matched analysis, patients with ACEi/ARB, β-blockers, and MRA had lower total in-hospital mortality and in-hospital mortality within 7 days, 14 days and 30 days. In the sub-group analysis, regardless of clinical characteristics including elderly people and cancer, patients treated with a combination of loop diuretics and neurohormonal blockers had significantly lower in-hospital mortality than matched patients. Conclusions : Our data indicate the benefits of guideline-directed medical therapy to loop diuretics in the management of HF. J. Med. Invest. 70 : 41-53, February, 2023

INTRODUCTION

Heart failure (HF) patients generally require use of oral loop diuretics to improve congestion (1). However, the clinical efficacy and safety of loop diuretics remain lacking. There is limited evidence from randomized control trials to decide the treatment of loop diuretics (2, 3). Exposure to higher doses of loop diuretics seems to be associated with worse outcomes (4, 5). Thus, current guidelines recommend using the minimum dose of loop diuretic required to improve fluid accumulation in the lungs (6).

Possible mechanisms of negative effects by loop diuretic use for prognosis include activation of the renin-angiotensin-aldosterone (RAAS) system, activation of the sympathetic nervous system, and worsening of renal function (7, 8). Therefore, when loop diuretics is used in congestive conditions, RAAS system inhibitors (angiotensin-converting enzyme inhibitor : ACEi or angiotensin receptor blocker : ARB), β-blockers and mineralocorticoid receptor antagonists (MRA) may be useful whenever possible especially in HF with reduced ejection fraction. However, there were few reports on the effect of combining loop diuretics and other neurohormonal blockers for the management of HF, with a sufficiently large sample size (9, 10). Our hypothesis was that the combination of loop diuretics and neurohormonal blockers

was associated with a decreased risk of in-hospital death in HF patients. Therefore, our aim of this study was to evaluate the mortality of patients receiving a combination therapy of diuretics and neurohormonal blockers compared with a matched cohort with monotherapy of loop diuretics, using registry data based on HF hospitalizations.

METHODS

Study population

The study population was composed of hospitalized patients between April 2015 and March 2017 in The Japanese Registry of All Cardiac and Vascular Diseases and the Diagnosis Procedure Combination (JROAD-DPC) database. JROAD-DPC is a nationwide registry, a medical database with information on admission and discharge for cardiovascular diseases, clinical examinations and treatment status, patient status and hospital overview. JROAD-DPC database integrates the information composed by JROAD-DPC data, with analysis data sets covering 3.6 million cases in 1,022 hospitals between April 2015 and March 2017. The identification of HF (I50.0, I50.1, I50.9) hospitalization was based on the International Classification of Diseases (ICD) -10 diagnosis codes. Data regarding patient age and sex, main diagnosis, comorbidity, medication at admission, length of hospitalization, and treatment content were extracted from the database. This sampling is similar to the method we have shown previously (11).

We recruited 294,943 patients hospitalized with HF. Diagnosis of HF was defined as the main diagnosis, admission-precipitating

diagnosis, or most resource-consuming diagnosis. We excluded patients with readmission cases (n=91,058), age <20 years (n=1403), death in 24 hours after admission because their medical histories were not properly interviewed (n=4,400), planned hospitalization to exclude the chronic phase of HF (n=22,451), lack of any data (n=82,986), no use of loop diuretics to focus on the congestive condition of HF at admission (n=13,960). To compare loop diuretics and loop diuretics + 1 drug combination therapy, we excluded patients with loop diuretics + 2 drugs and loop diuretics + 3 drugs (n=36,401). In the propensity matched cohort, total 42,284 (14,934 patients with loop diuretics and 13,311 patients with ACEi or ARB, 4561 patients with loop diuretics and β-blockers, and 9478 patients with loop diuretics and MRA) were recruited to assess hospital mortality for comparison between single and dual combination therapy (Figure 1).

The Institutional Review Board of the Tokushima University Hospital approved the study protocol (no. 3503). This review board waived the requirement for individual informed consent because information specific to individuals is not included. All methods were in accordance with the relevant guidelines and regulations. The procedures were followed in accordance with the "Declaration of Helsinki" and the ethical standards of the responsible committee on human experimentation.

Clinical Outcomes

The main outcome was in-hospital mortality (total number of deaths during hospitalization and death ≤7, 14, and 30 days after admission).

Sample Matching

Propensity score (PS) matching was used to reduce confounding effects related to differences in patient background. PS was estimated with a logistic regression model, with ACEi or ARB, β-blocker, and MRA as the dependent variable and the following 24 clinically relevant covariates ; age, sex, body mass index (BMI), smoking, New York Heart Association function-

al classification (NYHA), comorbidities (hypertension : HT, diabetes : DM, dyslipidemia : DL, atrial fibrillation/atrial flutter : Af/AFL, stroke, myocardial infarction : MI, peripheral vascular disease : PVD, renal disease, liver failure, chronic obstructive pulmonary disease : COPD, rheumatoid arthritis : RA, dementia, cancer), treatment (catecholamine, intra-aortic balloon pumping : IABP, percutaneous cardiopulmonary support : PCPS, ventilation, hemodialysis, percutaneous coronary intervention : PCI). These covariates were chosen for their potential association with reference to risk factors of heart failure and in-hospital mortality (12-14). Matching was performed by greedy-matching algorithm (ratio=1 : 1 without replacement), with a caliper of width 0.2 standard deviations of the logistic of the estimated propensity score. The absolute value of standardized differences less than 10% was considered to be a relatively small imbalance.

Statistical analysis

Continuous variables are expressed as mean±SD for parameters with normal distribution, as median (interquartile range ; IQR) for parameters with skewed distribution, and categorical variables as proportion (%). We checked characteristics between groups with and without combination therapy using standardized difference. After matching, we estimated the OR (odds ratio) for in-hospital mortality (total, within 7 days, 14 days and 30 days) using mixed-effects logistic regression model with each institute as a random effect. We also analyzed subgroups in the PS-matched cohort. Cumulative incidence analysis was used to plot the incidence–time curves with discharge alive as a competing risk, and the Gray test was used to analyze group differences in the occurrence of end point events (15). All statistical tests were 2-sided and p values less than 0.05 were considered statistically significant. Statistical analysis was performed using SAS version 9.4 and JMP 14.0 (SAS Institute Inc., Cary, NC).
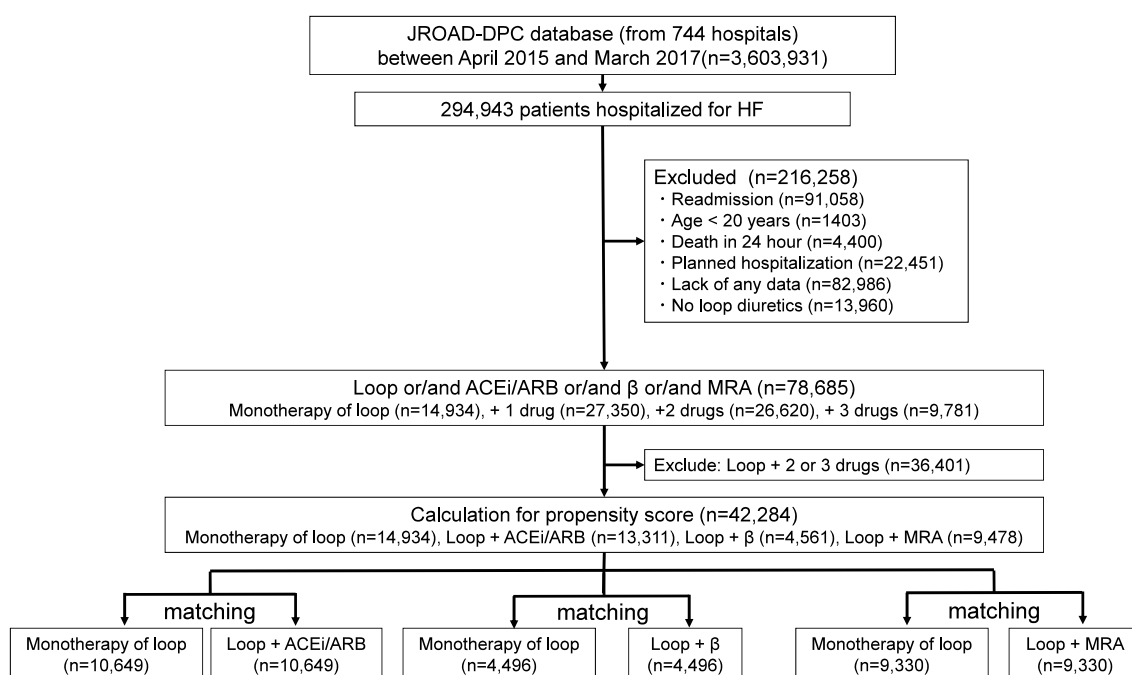

Figure 1. Flowchart of this study. HF, heart failure ; ACEi, angiotensin-converting enzyme inhibitor : ARB, angiotensin receptor blocker ; MRA, mineralocorticoid receptor antagonists.

RESULTS

Mortality among the combination therapies

Before propensity matching, we assessed the mortality among the combination therapies (monotherapy of loop diuretics, loop diuretics + ACEi/ARB, + β-blocker, + MRA, + ACEi/ARB and β-blocker, + ACEi/ARB and MRA, + β-blocker and MRA, and + ACEi/ARB, β-blocker, and MRA). Characteristics of 8 groups are shown in Supplemental Table 1. Among 8 groups, patients with monotherapy of loop diuretics had significantly worst outcomes (P <0.001). The ranks of poor outcomes were as follows. 1. monotherapy of loop diuretics, 2. +β-blocker, 3. +MRA, 4. +β-blocker and MRA, 5. +ACEi/ARB, 6. +β-blocker and ACEi/ARB, 7. +ACEi/ARB and MRA, 8. +ACEi/ARB, β-blocker, and MRA (Figure 2).

Comparison between monotherapy of loop diuretics vs loop diuretics and ARB/ACEi

A total of 52.4% of patients was male. Mean age was 81±12 years. Patients with loop diuretics + ARB/ACEi were more likely to have a history of hypertension, diabetes mellitus and dyslipidemia. There are differences in age, gender, BMI, smoking, dementia, catecholamine use, and percutaneous coronary intervention between two groups. After propensity score matching, 21,298 patients were included in the survival analysis. In the matched cohort, there were no differences between groups for clinical comorbidities, and treatments (Supplemental Table 2). The balance of each covariate before and after matching between the 2 groups was evaluated using standardized differences. The area under the curve was 0.67 and the consistency of PS densities was matched after matching.

In-hospital mortality, mortality within 7 days, 14 days, and 30 days of hospitalization are summarized in Table 1. Even after matching, patients with loop diuretics and ARB/ACEi had significantly lower in-hospital mortality (5.9% vs. 15.9%, P<0.001 ; OR, 0.33, 95% CI : 0.30-0.37), mortality within 7 days of hospitalization (0.8% vs. 5.3%, P<0.001 ; OR, 0.15, 95% CI : 0.12-0.19), within 14 days (1.9% vs. 9.1%, P<0.001 ; OR, 0.19, 95% CI : 0.16-0.22), and within 30 days (3.8% vs. 13.0%, P<0.001 ; OR, 0.26, 95% CI : 0.23-0.29). Mortality curves of in-hospital death were shown in Figure 3A. Combination therapy of loop diuretics and ARB/ACEi was strongly associated with mortality rate (P <0.001). Mortality in each sub-group, forest plots of odds ratio are shown in Figure 3B. Regardless of clinical characteristics, patients with combination therapy of loop diuretics and ARB/ACEi had significantly lower in-hospital mortality than matched patients on monotherapy of loop diuretics.

Comparison between monotherapy of loop diuretics vs loop diuretics and β-blocker

A total of 49.5% of patients in this study was male. Mean age was 82±11 years. Patients with loop diuretics + β-blocker were more likely to have a history of atrial fibrillation/flutter. There are differences in age and chronic kidney disease between two groups. After propensity score matching, 8,992 patients were included in the survival analysis. In the matched cohort, there were no differences between groups for all parameters (Supplemental Table 3). The balance of each covariate before and after matching between the 2 groups was evaluated using standardized differences. The area under the curve was 0.68 and the consistency of PS densities was matched after matching.

In-hospital mortality, mortality within 7 days, 14 days, and 30 days of hospitalization are summarized in Table 2. Even after matching, patients with loop diuretics and β-blocker had

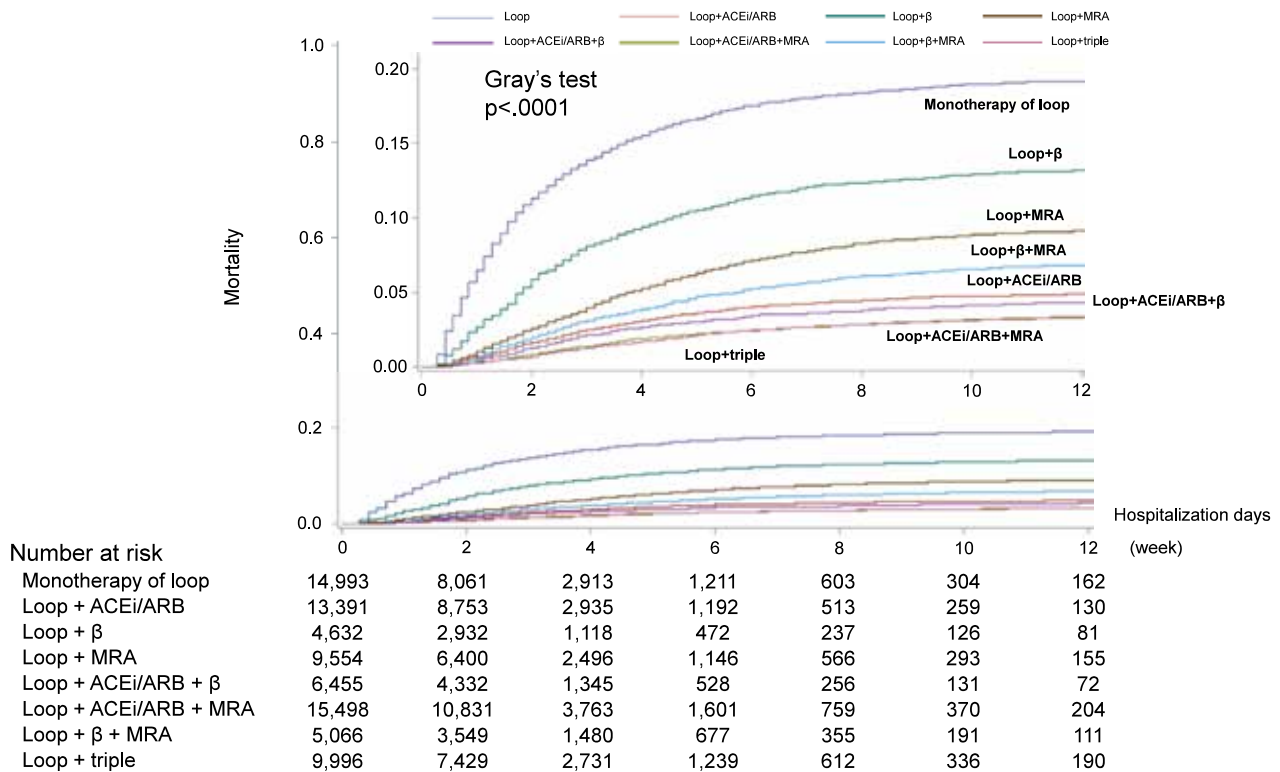| Number at risk	0	2	4	6	8	10	12 (week)
Monotherapy of loop	14,993	8,061	2,913	1,211	603	304	162
Loop + ACEi/ARB	13,391	8,753	2,935	1,192	513	259	130
Loop + β	4,632	2,932	1,118	472	237	126	81
Loop + MRA	9,554	6,400	2,496	1,146	566	293	155
Loop + ACEi/ARB + β	6,455	4,332	1,345	528	256	131	72
Loop + ACEi/ARB + MRA	15,498	10,831	3,763	1,601	759	370	204
Loop + β + MRA	5,066	3,549	1,480	677	355	191	111
Loop + triple	9,996	7,429	2,731	1,239	612	336	190

Figure 2. Mortality curves of in-hospital death among 8 groups. Among 8 groups, patients with monotherapy of loop diuretics had significantly worst outcomes (P <0.001). See abbreviations as in Figure 1.

Table 1. In-hospital mortality for propensity score matching for combination of ACEi/ARB

Before Matching

	Loop only	Loop + ACEi/ARB	OR	lower	upper	p
Total	2927 (19.6)	674 (5.1)	0.22	0.20	0.24	<.0001
7 days	971 (6.5)	95 (0.7)	0.10	0.08	0.13	<.0001
14 days	1687 (11.3)	221 (1.7)	0.13	0.11	0.15	<.0001
30 days	2389 (16.0)	436 (3.3)	0.18	0.16	0.20	<.0001

After Matching

	Loop only	Loop + ACEi/ARB	OR	lower	upper	p
Total	1688 (15.9)	629 (5.9)	0.33	0.30	0.37	<.0001
7 days	560 (5.3)	89 (0.8)	0.15	0.12	0.19	<.0001
14 days	967 (9.1)	198 (1.9)	0.19	0.16	0.22	<.0001
30 days	1382 (13.0)	399 (3.8)	0.26	0.23	0.29	<.0001

See abbreviations as in Supplemental Table 1.

Table 2. In-hospital mortality for propensity score matching for combination of β-blockers

Before Matching

	Loop only	Loop + β	OR	lower	upper	p
Total	2927 (19.6)	627 (13.8)	0.65	0.60	0.72	<.0001
7 days	971 (6.5)	123 (2.7)	0.40	0.33	0.48	<.0001
14 days	1687 (11.3)	270 (5.9)	0.49	0.43	0.56	<.0001
30 days	2389 (16.0)	446 (9.8)	0.57	0.51	0.63	<.0001

After Matching

	Loop only	Loop + β	OR	lower	upper	p
Total	796 (17.7)	619 (13.8)	0.74	0.66	0.83	<.0001
7 days	258 (5.7)	121 (2.7)	0.45	0.36	0.57	<.0001
14 days	468 (10.4)	266 (5.9)	0.54	0.46	0.63	<.0001
30 days	645 (14.4)	441 (9.8)	0.65	0.57	0.74	<.0001

See abbreviations as in Supplemental Table 1.

significantly lower in-hospital mortality (13.8% vs. 17.7%, P<0.001 ; OR, 0.74, 95% CI : 0.66-0.83), mortality within 7 days of hospitalization (2.7% vs. 5.7%, P<0.001 ; OR, 0.45, 95% CI : 0.36-0.57), within 14 days (5.9% vs. 10.4%, P<0.001 ; OR, 0.54, 95% CI : 0.46-0.63), and within 30 days (9.8% vs. 14.4%, P<0.001 ; OR, 0.65, 95% CI : 0.57-0.74). Mortality curves of in-hospital death were shown in Figure 4A. Combination therapy with loop diuretics and β-blocker was strongly associated with mortality rate (P <0.001). Mortality in each sub-group, forest plots of odds ratio are shown in Figure 4B. Mortality in patients with chronic kidney disease (OR, 0.89, 95% CI : 0.67-1.18, P=0.42) was not affected by the combination therapy of diuretics and β-blocker.

Comparison between monotherapy of loop diuretics vs loop diuretics and MRA

A total of 48.8% of patients in this study were male. Mean age was 82±11 years. There are differences for atrial fibrillation/flatter and chronic kidney disease between the two groups. After propensity score matching, 18,660 patients were included in the survival analysis. In the matched cohort, there were no differences between groups for all parameters (Supplemental Table 4). The balance of each covariate before and after matching between the 2 groups was evaluated using standardized differences. Area under the curve was 0.61 and the consistency of PS densities was matched after matching.

In-hospital mortality, mortality within 7 days, 14 days, and 30 days of hospitalization are summarized in Table 3. Even after matching, patients with loop diuretics and MRA had significantly lower in-hospital mortality (9.7% vs. 18.2%, P<0.001 ; OR, 0.48, 95% CI : 0.45-0.53), mortality within 7 days of hospitalization (1.1% vs. 6.1%, P<0.001 ; OR, 0.17, 95% CI : 0.14-0.21), within 14 days (2.7% vs. 10.6%, P<0.001 ; OR, 0.23, 95% CI : 0.20-0.27), and within 30 days (5.6% vs. 15.0%, P<0.001 ; OR, 0.34, 95% CI : 0.30-0.38). Mortality curves of in-hospital death were shown in Figure 5A. Combination therapy of loop diuretics and MRA was strongly associated with mortality rate (P<0.001). Mortality in each sub-group, forest plots of odds ratio are shown in Figure 5B. Regardless of clinical characteristics, patients with combination therapy of loop diuretics and MRA had significantly lower in-hospital mortality than matched patients on monotherapy of loop diuretics.

Number at risk						
Monotherapy of loop	10,649	6,091	2,218	964	468	234	138
Loop + ACEi/ARB	10,649	7,447	2,802	1,182	570	274	147

Figure 3A

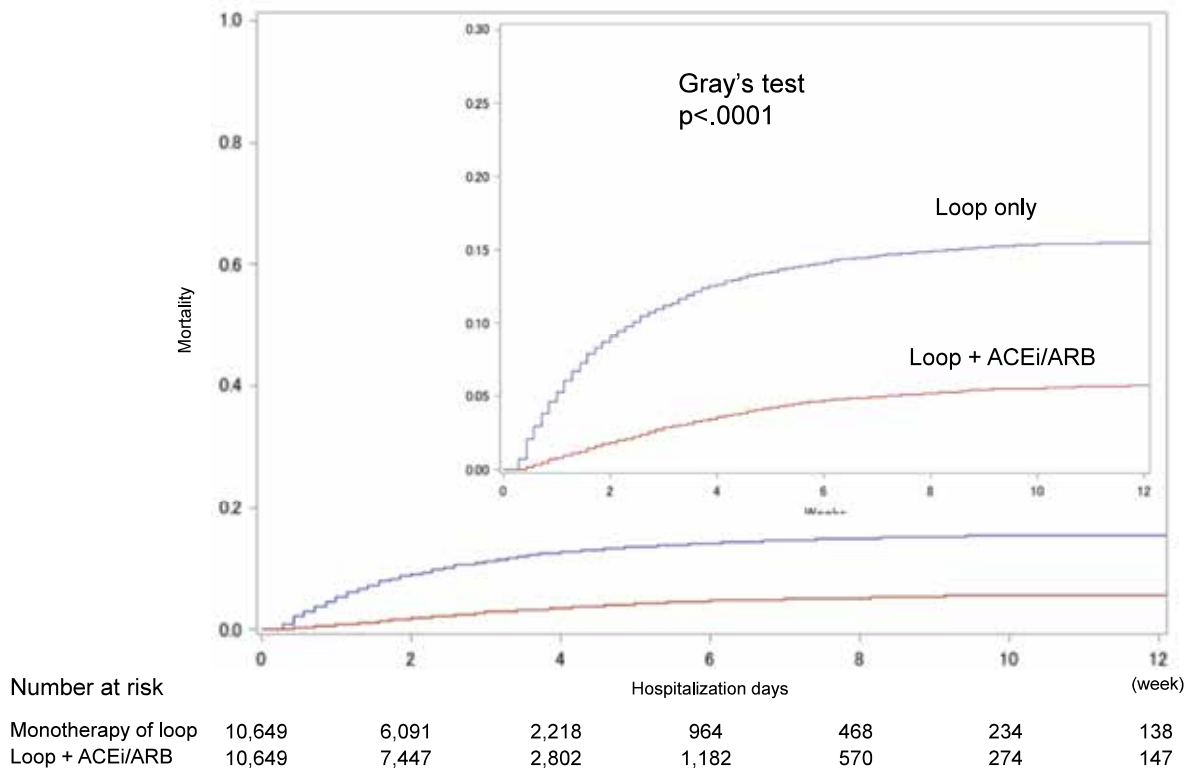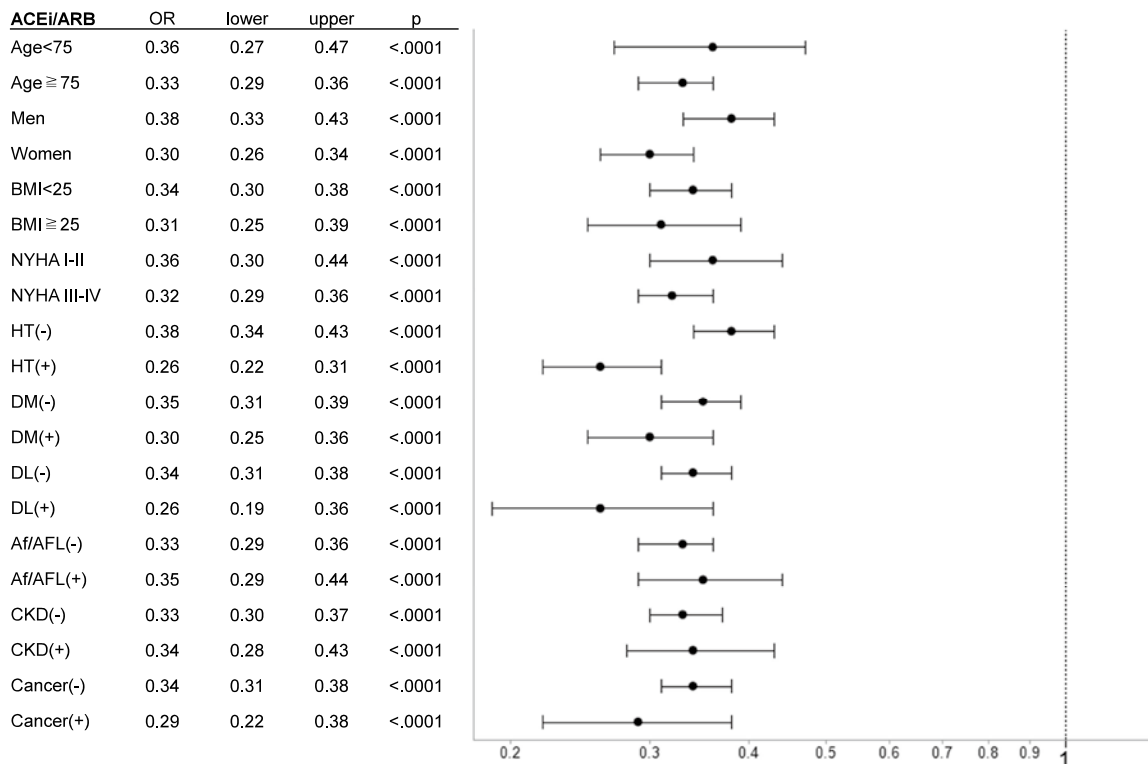| ACEi/ARB	OR	lower	upper	p
Age<75	0.36	0.27	0.47	<.0001
Age≧75	0.33	0.29	0.36	<.0001
Men	0.38	0.33	0.43	<.0001
Women	0.30	0.26	0.34	<.0001
BMI<25	0.34	0.30	0.38	<.0001
BMI≧25	0.31	0.25	0.39	<.0001
NYHA I-II	0.36	0.30	0.44	<.0001
NYHA III-IV	0.32	0.29	0.36	<.0001
HT(-)	0.38	0.34	0.43	<.0001
HT(+)	0.26	0.22	0.31	<.0001
DM(-)	0.35	0.31	0.39	<.0001
DM(+)	0.30	0.25	0.36	<.0001
DL(-)	0.34	0.31	0.38	<.0001
DL(+)	0.26	0.19	0.36	<.0001
Af/AFL(-)	0.33	0.29	0.36	<.0001
Af/AFL(+)	0.35	0.29	0.44	<.0001
CKD(-)	0.33	0.30	0.37	<.0001
CKD(+)	0.34	0.28	0.43	<.0001
Cancer(-)	0.34	0.31	0.38	<.0001
Cancer(+)	0.29	0.22	0.38	<.0001

Figure 3B

Figure 3. Mortality curves (A) and odds ratio (B) of in-hospital death between monotherapy of loop diuretics and +ACEi/ARB. Patients with combination therapy of loop diuretics and ACEi/ARB had significantly lower in-hospital mortality than matched patients with monotherapy of loop diuretics. Dots and lines mean OR and 95% CI, respectively.

Number at risk						
Monotherapy of loop	4,496	2,550	952	417	212	114	65
Loop + β-blocker	4,496	3,030	1,226	531	263	150	86

Figure 4A

β	OR	lower	upper	p
Age<75	0.66	0.48	0.91	0.0105
Age≧75	0.76	0.67	0.86	<.0001
Men	0.76	0.64	0.90	0.0015
Women	0.73	0.63	0.85	0.0009
BMI<25	0.76	0.67	0.86	<.0001
BMI≧25	0.67	0.50	0.89	0.0059
NYHA I-II	0.71	0.57	0.89	0.0029
NYHA III-IV	0.75	0.65	0.86	<.0001
HT(-)	0.73	0.64	0.84	<.0001
HT(+)	0.74	0.61	0.90	0.0031
DM(-)	0.74	0.65	0.84	<.0001
DM(+)	0.75	0.58	0.97	0.0262
DL(-)	0.75	0.67	0.85	<.0001
DL(+)	0.60	0.40	0.89	0.0101
Af/AFL(-)	0.82	0.70	0.95	0.0106
Af/AFL(+)	0.66	0.56	0.79	<.0001
CKD(-)	0.72	0.63	0.81	<.0001
CKD(+)	0.89	0.67	1.18	0.4247
Cancer(-)	0.77	0.68	0.87	<.0001
Cancer(+)	0.59	0.43	0.81	0.0012

Figure 4B

Figure 4. Mortality curves (A) and odds ratio (B) of in-hospital death between monotherapy of loop diuretics and +β-blocker. Patients with combination therapy of loop diuretics and β-blocker had significantly lower in-hospital mortality than matched patients with monotherapy of loop diuretics. Dots and lines mean OR and 95% CI, respectively.
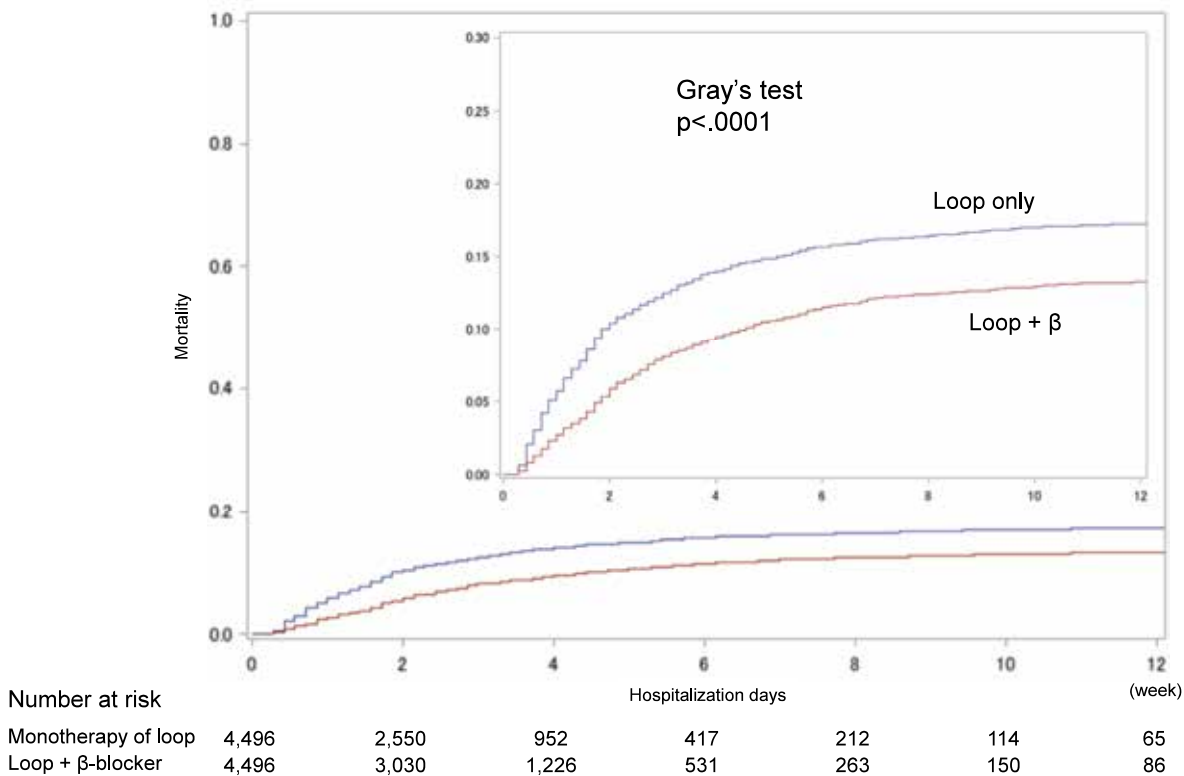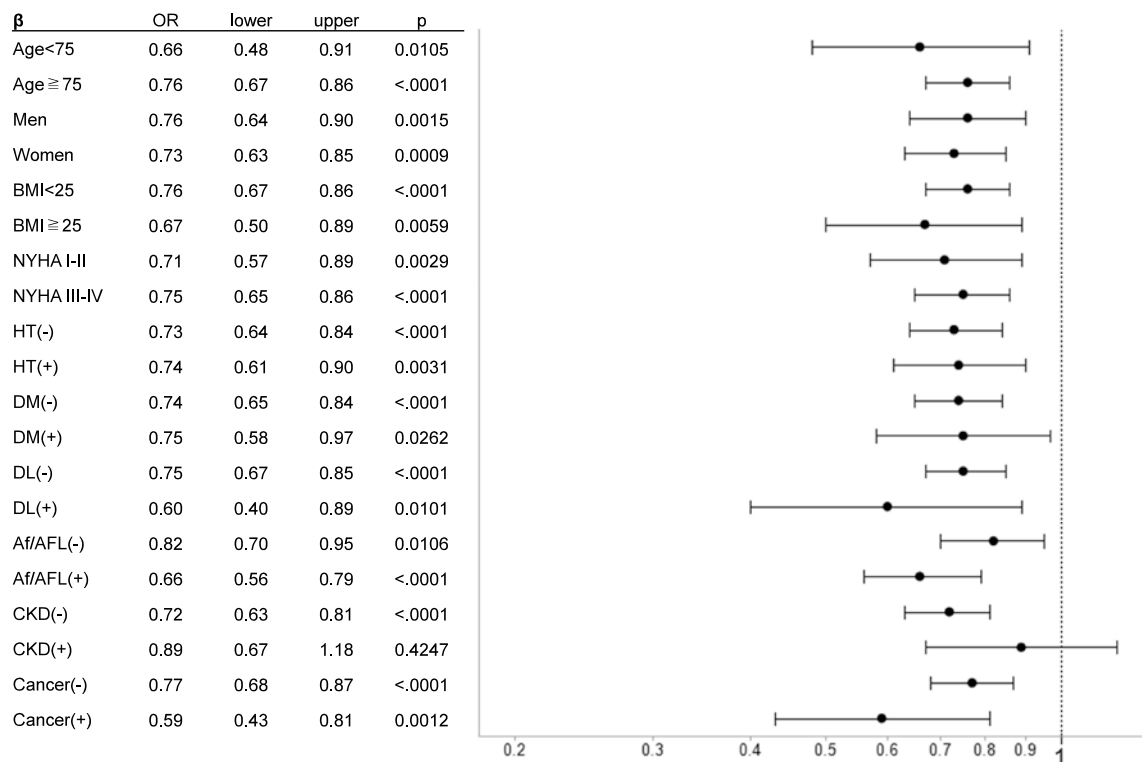
Number at risk

Monotherapy of loop	9,330	5,301	1,926	826	416	215	121
Loop + MRA	9,330	6,607	2,733	1,313	655	348	199

Figure 5A

MRA	OR	lower	upper	p
Age<75	0.62	0.48	0.79	<.0001
Age≧75	0.47	0.43	0.51	<.0001
Men	0.54	0.47	0.61	<.0001
Women	0.45	0.40	0.50	<.0001
BMI<25	0.49	0.45	0.54	<.0001
BMI≧25	0.45	0.36	0.57	<.0001
NYHA I-II	0.54	0.46	0.64	<.0001
NYHA III-IV	0.46	0.42	0.51	<.0001
HT(-)	0.50	0.45	0.56	<.0001
HT(+)	0.43	0.37	0.51	<.0001
DM(-)	0.46	0.42	0.50	<.0001
DM(+)	0.61	0.50	0.74	<.0001
DL(-)	0.48	0.44	0.53	<.0001
DL(+)	0.52	0.39	0.70	<.0001
Af/AFL(-)	0.49	0.44	0.54	<.0001
Af/AFL(+)	0.47	0.40	0.55	<.0001
CKD(-)	0.48	0.44	0.52	<.0001
CKD(+)	0.55	0.42	0.71	<.0001
Cancer(-)	0.48	0.44	0.53	<.0001
Cancer(+)	0.48	0.38	0.60	<.0001

Figure 5B

Figure 5.   Mortality curves (A) and odds ratio (B) of in-hospital death between monotherapy of loop diuretics and +MRA. Patients with combination therapy of loop diuretics and MRA had significantly lower in-hospital mortality than matched patients with monotherapy of loop diuretics. Dots and lines mean OR and 95% CI, respectively.
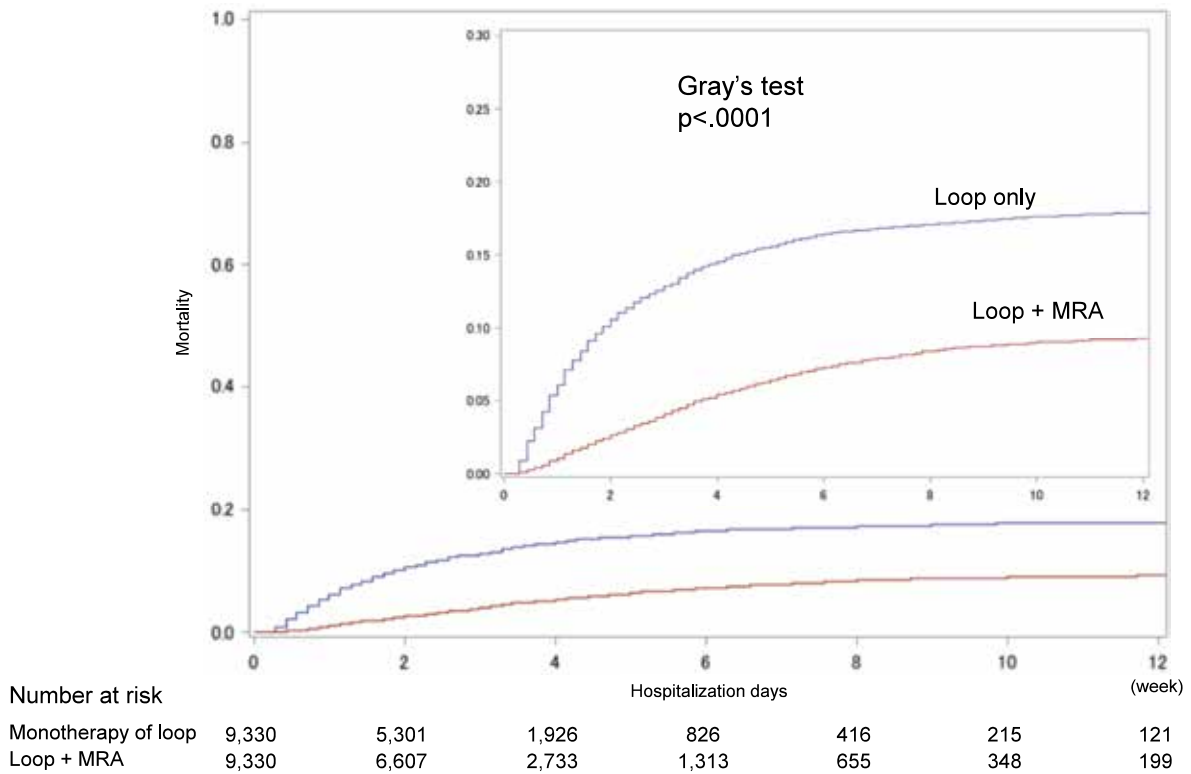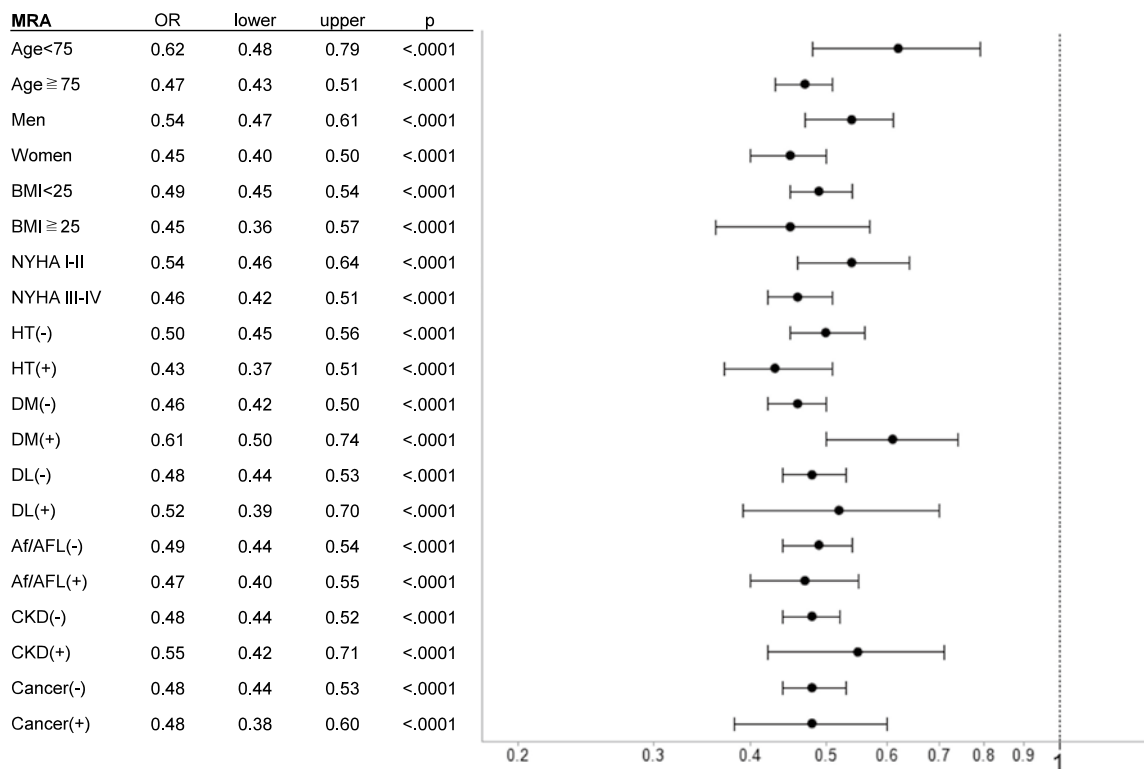
Table 3. In-hospital mortality for propensity score matching for combination of MRA

Before Matching

	Loop only	Loop + MRA	OR	lower	upper	p
Total	2927 (19.6)	916 (9.7)	0.44	0.41	0.48	<.0001
7 days	971 (6.5)	100 (1.1)	0.15	0.12	0.19	<.0001
14 days	1687 (11.3)	249 (2.6)	0.21	0.18	0.24	<.0001
30 days	2389 (16.0)	527 (5.6)	0.31	0.28	0.34	<.0001

After Matching

	Loop only	Loop + MRA	OR	lower	upper	p
Total	1699 (18.2)	909 (9.7)	0.48	0.45	0.53	<.0001
7 days	565 (6.1)	100 (1.1)	0.17	0.14	0.21	<.0001
14 days	987 (10.6)	248 (2.7)	0.23	0.20	0.27	<.0001
30 days	1400 (15.0)	525 (5.6)	0.34	0.30	0.38	<.0001

See abbreviations as in Supplemental Table 1.

DISCUSSION

The main findings of this study were 1) in the non-matched cohort, patients on monotherapy of loop diuretics had the worst survival, meanwhile patients receiving loop diuretics and triple therapy (ACEi/ARB + β-blockers + MRA) had the best outcome ; 2) in the PS-matched cohort, HF patients with combination therapy of loop diuretics and neurohormonal blockers had significantly lower in-hospital mortality compared with monotherapy of loop diuretics ; 3) in spite of clinical characteristics such as old age and cancer, the effects of combination therapy were consistent in the sub-group analysis. Our data indicate the benefits of combining neurohormonal blockers with loop diuretics in the management of HF.

Impacts of loop diuretics on HF

Although current guidelines recommend the minimum dose of loop diuretic should be used in HF, there were no randomized trials to assess the evidence of loop diuretics in the prognosis. Some small prospective and retrospective studies showed the connection of loop diuretics and hospital mortality in patients with HF. The risk of cardiovascular events was significantly increased in patients with non–potassium-sparing diuretics (16, 17). The association between high doses of loop diuretics and poor outcomes was described in patients enrolled in the Amlodipine Survival Evaluation trial. There was a significant association between a higher than median dose of loop diuretics (80 mg) and all-cause mortality/sudden death (18). Negative effects of loop diuretics have been observed in these previous reports.

Mechanisms of neurohormonal blockers on HF under loop diuretics

Activation of the renin-angiotensin-aldosterone system and sympathetic nervous system by loop diuretics plays an important role in the pathophysiology of HF. This mechanism may be associated with HF progression (19, 20). Diuretics for patients without significant fluid retention, intravascular volume constriction, or decreased left ventricular filling pressure can lead the low cardiac output. Loop diuretics, especially furosemide, activate the renin-angiotensin-aldosterone system in HF patients. Administration of loop diuretics causes a significant increase in plasma renin, angiotensin II, and aldosterone concentrations, resulting in activation of neurohormones (21). Furthermore, whereas HF alone did not increase either plasma renin or aldo-

sterone, furosemide treatment for 1 month resulted in significant neurohumoral activation (22). Prolonged exposure to aldosterone can adversely affect left ventricular function, causing reactive myocardial fibrosis and a variety of other adverse effects. Our results were consistent with these backgrounds. ACEi/ARB and MRA could be useful to treat HF with loop diuretics, regardless of any clinical characteristics in this large dataset.

The cardioprotective effects of beta-blockers are controversial in HF management with diuretics. A previous meta-analysis has shown that beta-blockers significantly reduce blood pressure, but are not effective in preventing coronary artery disease, cardiovascular disease, or all-cause mortality (23). In our analysis, the effectiveness of additional β-blocker was relatively low compared with ACEi/ARB and MRA. On the other hand, in the non-matched cohort, triple therapy (ACEi/ARB + β-blockers + MRA) had the best outcomes. In the clinical setting, firstly, we may try to add the ACEi/ARB or MRA. Beta-blockers can be used as a second option in HF under the treatment of loop diuretics.

Clinical implication

Based on our results from a large HF cohort, patients with combination therapy had lower in-hospital mortality. Although the previous studies examined and defined a linkage between loop diuretic and HF prognosis, to the best of our knowledge, this is the first study to report a positive effect for combination therapy of neurohormonal blockers on mortality in a large-scale cohort.

Limitations

The study based on ICD codes has several limitations. First, we analyzed only patients with HF hospitalized in the cardiovascular institutes, which might lead to selection bias. Second, the database has no laboratory and echocardiographic data including ejection fraction to assess the detailed prognosis of HF in each patient. Generally, neurohormonal blockers have not been shown to improve survival in HF preserved ejection fraction, but serve as a life-saving medical therapy in HF reduced ejection fraction. In our entire cohort including both phenotypes, the patients with combination therapy had lower in-hospital mortality. Third, the database has no information on the specific doses of loop diuretics administered. There were no data on the congestion status and the appropriate use of loop diuretics is unclear. Forth, propensity score matching reports potential dif-

ferences between groups with some degree of accuracy. Despite the application of propensity matching to the groups of patients to be compared, there may be hidden biases related to patient selection in this non-randomized observational study because of unadjusted and unknown differences. To address this issue, we used therapeutic devices and catecholamine medication as markers of HF severity. In this study, all-cause mortality was the primary endpoint. Since our patient population is known to be at high risk, the most probable cause of death is HF. Fifth, the accuracy of the diagnosis is not perfect, because these are less validated in the DPC database compared with planned prospective studies. However, this DPC dataset has been validated in the previous study (24) and we believed that the consistency is relatively high for this dataset.

Conclusions

Our data indicate the benefits of guideline-directed medical therapy to loop diuretics in the management of HF.

CONFLICTS OF INTEREST

None

CONTRIBUTORS

KK conceived the idea for this study. Y Okushi and Y Okayama conducted the data analyses. The initial draft of the manuscript was produced by KK. All authors were involved in interpreting the results and writing the manuscript. All authors read and approved the final manuscript.

DISCLOSURES

The authors declare that there are no conflicts of interest.

FUNDING

IRB INFORMATION

The Institutional Review Board of the Tokushima University Hospital approved the study protocol (no. 3503).

REFERENCES

1. Kapelios CJ, Malliaras K, Kaldara E, Vakrou S, Nanas JN : Loop diuretics for chronic heart failure : a foe in disguise of a friend? Eur Heart J Cardiovasc Pharmacother 4 : 54-63, 2018

2. Leto L, Aspromonte N, Feola M : Efficacy and safety of loop diuretic therapy in acute decompensated heart failure : a clinical review. Heart Fail Rev 19 : 237-46, 2014

3. Trullàs JC, Morales-Rull JL, Casado J, Ramírez AF, Manzano L, Formiga F : Rationale and design of the "Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) Trial : " a double-blind, randomized, place-bo-controlled study to determine the effect of combined diuretic therapy (loop diuretics with thiazide-type diuretics) among patients with decompensated heart failure. Journal of cardiac failure 22 : 529-536, 2016

4. Eshaghian S, Horwich TB, Fonarow GC : Relation of loop diuretic dose to mortality in advanced heart failure. Am J Cardiol 97 : 1759-64, 2006

5. Okabe T, Yakushiji T, Kido T, Oyama Y, Igawa W, Ono M, Ebara S, Yamashita K, Yamamoto MH, Saito S : The association between high-dose loop diuretic use at discharge and cardiovascular mortality in patients with heart failure. ESC Heart Failure 5 : 87-94, 2018

6. Tsutsui H, Isobe M, Ito H, Ito H, Okumura K, Ono M, Kitakaze M, Kinugawa K, Kihara Y, Goto Y, Komuro I, Saiki Y, Saito Y, Sakata Y, Sato N, Sawa Y, Shiose A, Shimizu W, Shimokawa H, Seino Y, Node K, Higo T, Hirayama A, Makaya M, Masuyama T, Murohara T, Momomura SI, Yano M, Yamazaki K, Yamamoto K, Yoshikawa T, Yoshimura M, Akiyama M, Anzai T, Ishihara S, Inomata T, Imamura T, Iwasaki YK, Ohtani T, Onishi K, Kasai T, Kato M, Kawai M, Kinugasa Y, Kinugawa S, Kuratani T, Kobayashi S, Sakata Y, Tanaka A, Toda K, Noda T, Nochioka K, Hatano M, Hidaka T, Fujino T, Makita S, Yamaguchi O, Ikeda U, Kimura T, Kohsaka S, Kosuge M, Yamagishi M, Yamashina A, Japanese Circulation S, the Japanese Heart Failure Society Joint Working G : JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure- Digest Version. Circ J 83 : 2084-2184, 2019

7. ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, Voors AA : Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy. Nat Rev Cardiol 12 : 184-92, 2015

8. Ellison DH : Clinical Pharmacology in Diuretic Use. Clinical journal of the American Society of Nephrology : CJASN 14 : 1248-1257, 2019

9. Dormans TP, Gerlag PG, Russel FG, Smits P : Combination diuretic therapy in severe congestive heart failure. Drugs 55 : 165-72, 1998

10. Casu G, Merella P : Diuretic Therapy in Heart Failure - Current Approaches. Eur Cardiol 10 : 42-47, 2015

11. Kusunose K, Okushi Y, Okayama Y, Zheng R, Abe M, Nakai M, Sumita Y, Ise T, Tobiume T, Yamaguchi K, Yagi S, Fukuda D, Yamada H, Soeki T, Wakatsuki T, Sata M : Association between Vitamin D and Heart Failure Mortality in 10,974 Hospitalized Individuals. Nutrients 13, 2021

12. Win S, Hussain I, Hebl VB, Dunlay SM, Redfield MM : Inpatient Mortality Risk Scores and Postdischarge Events in Hospitalized Heart Failure Patients : A Community-Based Study. Circ Heart Fail 10, 2017

13. Peterson PN, Rumsfeld JS, Liang L, Albert NM, Hernandez AF, Peterson ED, Fonarow GC, Masoudi FA, American Heart Association Get With the Guidelines-Heart Failure P : A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association get with the guidelines program. Circ Cardiovasc Qual Outcomes 3 : 25-32, 2010

14. Hannan EL, Wu C, Bennett EV, Carlson RE, Culliford AT, Gold JP, Higgins RS, Smith CR, Jones RH : Risk index for predicting in-hospital mortality for cardiac valve surgery. Ann Thorac Surg 83 : 921-9, 2007

15. Austin PC, Lee DS, Fine JP : Introduction to the analysis of survival data in the presence of competing risks. Circulation 133 : 601-609, 2016

16. Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ : Diuretics and risk of arrhythmic death in patients with

left ventricular dysfunction. Circulation 100 : 1311-5, 1999

17. Domanski M, Norman J, Pitt B, Haigney M, Hanlon S, Peyster E, Studies of Left Ventricular D : Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol 42 : 705-8, 2003

18. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB, Frid DJ, Nye RG, Pressler ML, Wertheimer JH, Packer M, Evaluation PIPRAS : Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J 144 : 31-8, 2002

19. Furumatsu Y, Nagasawa Y, Tomida K, Mikami S, Kaneko T, Okada N, Tsubakihara Y, Imai E, Shoji T : Effect of renin-angiotensin-aldosterone system triple blockade on non-diabetic renal disease : addition of an aldosterone blocker, spironolactone, to combination treatment with an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker. Hypertension Research 31 : 59-67, 2008

20. Miura M, Sugimura K, Sakata Y, Miyata S, Tadaki S,

Yamauchi T, Onose T, Tsuji K, Abe R, Oikawa T : Prognostic Impact of Loop Diuretics in Patients With Chronic Heart Failure–Effects of Addition of Renin-Angiotensin-Aldosterone System Inhibitors and β-Blockers–. Circulation Journal : CJ-16-0216, 2016

21. Ikram H, Chan W, Espiner EA, Nicholls MG : Haemodynamic and hormone responses to acute and chronic frusemide therapy in congestive heart failure. Clin Sci (Lond) 59 : 443-9, 1980

22. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P : Untreated heart failure : clinical and neuroendocrine effects of introducing diuretics. Br Heart J 57 : 17-22, 1987

23. Messerli FH, Grossman E, Goldbourt U : Are β-blockers efficacious as first-line therapy for hypertension in the elderly? : a systematic review. Jama 279 : 1903-1907, 1998

24. Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H : Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. J Epidemiol 27 : 476-482, 2017

Supplemental Table 1.   Baseline characteristics of 8 groups.

	Loop only	Loop+ACEi/ ARB	Loop+β	Loop+MRA	Loop+ACEi/ ARB+β	Loop+ACEi/ ARB+MRA	Loop+β+ MRA	Loop+triple
Number	14,934	13,311	4,561	9,478	6,455	15,099	5,066	9,781
Age (years)	82±11	79±12	80±11	81±12	77±12	77±13	78±12	75±13
Male (%)	49.8	55.2	48.6	47.2	55.5	54.5	46.8	53.6
BMI	22.1±4.8	23.2±5.7	22.3±4.3	21.8±4.4	23.5±4.7	23.1±4.9	22.2±5.7	23.4±4.9
NYHA I	14.9	11.4	12.6	12.5	10.7	9.8	10.5	9.6
II	22.9	24	23.3	23.6	24.2	22.8	23.5	22.9
III	29.6	32.6	32.4	33.2	31.8	33.5	35.5	33
IV	32.7	32.1	32.7	30.8	33.3	33.9	30.5	34.5
Comrbidities (%)								
HT	39.3	61.6	44.2	42.6	64.1	62.6	45.7	62.5
DM	25.2	33	22.2	22.2	30.7	29.2	20	26.8
Af/AFL	26.1	25.5	55.1	33.6	47.2	29.6	61.7	50.2
MI	9.6	12.1	7.9	9.9	10.1	13.1	8.1	10.5
CKD	19.5	19.1	14.6	8.8	12.8	7.4	6.9	5.9
Hemodialysis	4.5	4.8	4	0.7	2.8	0.7	0.8	0.7
Cancer	12.1	11.2	11.5	12.1	9.9	10.3	11.5	10.1
Treatment (%)								
Cathechoramines	14.1	10.2	15.5	14.6	10.8	12.4	16.4	15
IABP	0.6	0.8	0.9	0.8	1	1.4	1.3	1.9
PCPS	0.2	0.1	0.1	0.1	0.2	0.1	0.1	0.2
Ventilator	19.7	23.3	20.9	17.1	25.4	25.1	21.6	27.4

Data are presented as percentage of patients or median. Abbreviations : ACEi, angiotensin-converting enzyme inhibitor ; ARB, angiotensin receptor blocker ; β, β-blocker ; MRA, mineralocorticoid receptor antagonists ; BMI, body mass index ; NYHA, New York heart association functional class ; HT, hypertension ; Af, atrial fibrillation ; AFL, atrial flatter ; MI, myocardial infarction ; CKD, chronic kidney disease ; IABP, intra-aortic balloon pumping ; PCPS, percutaneous cardiopulmonary system.

Supplemental Table 2.   Baseline characteristics of the study population

		Non-Matching			*Matching*		
	All	Loop only	Loop + ACEi/ARB	Std.diff	Loop Only	Loop + ACEi/ARB	Std.diff
	(n=28,245)	(n=14,934)	(n=13,311)		(n=10,649)	(n=10,649)	
Age	81±12	82±11	79±12	25.5	81±12	81±11	0.8
Male (%)	52.4	49.8	55.3	-10.9	52.7	52.6	0.1
BMI	22.6±5.3	22.1±4.8	23.2±5.7	-21.5	22.7±4.6	22.7±4.3	0.2
Smoking (%)	28.8	26.3	31.7	-11.9	29.1	29.2	-0.2
NYHA I	13.3	14.9	11.4	10.3	12.4	12.6	-0.5
II	23.3	22.8	23.9	-2.6	23.9	23.7	0.6
III	31.0	29.6	32.6	-6.5	31.9	31.6	0.7
IV	32.4	32.7	32.0	1.4	31.8	32.1	-0.8
Comrbidities (%)							
HT	49.8	39.4	61.5	-45.5	53.4	53.2	0.3
DM	28.9	25.2	33.0	-17.3	29.3	29.8	-1.1
DL	16.7	12.6	21.4	-23.6	16.3	16.6	-0.7
Stroke	8.6	9.3	7.8	5.4	8.5	8.6	-0.6
Af/AFL	25.6	26.0	25.2	1.8	26.2	26.4	-0.4
MI	10.8	9.6	12.1	-7.9	10.8	11.1	-0.8
HCM	2.1	1.5	2.7	-8.7	1.7	2.5	-5.6
DCM	0.9	0.8	0.9	-0.9	0.9	0.9	0.6
Amyroid	0.1	0.1	0.1	0.3	0.1	0.1	0.6
Sarcoid	0.2	0.1	0.3	-2.5	0.2	0.2	-1.6
PVD	3.7	3.4	4.1	-3.3	3.7	3.9	-0.7
CKD	19.4	19.5	19.2	1.0	20.2	19.6	1.4
Hemodialysis	4.7	4.5	4.8	-1.4	4.9	4.7	0.9
Liver failure	0.1	0.1	0.1	1.9	0.1	0.1	<0.1
COPD	7.6	8.3	6.8	5.8	7.5	7.6	-0.1
Cancer	11.7	12.1	11.2	2.7	11.6	11.8	-0.6
RA	1.4	1.6	1.2	3.8	1.3	1.3	-0.8
Dementia	6.7	7.8	5.4	10.0	6.2	6.3	-0.4
Treatment (%)							
Cathechoramines	12.3	14.1	10.2	12.1	10.7	11.4	-2.0
IABP	0.7	0.6	0.8	-3.2	0.6	0.7	-0.9
PCPS	0.2	0.2	0.1	1.6	0.1	0.1	-0.3
Ventilator	21.4	19.7	23.4	-8.8	21.1	21.5	-0.8
PCI	4.1	2.5	5.9	-17.4	3.4	3.6	-1.3

Data are presented as percentage of patients, median or mean±standard deviation. A standardized difference of < 10% suggests adequate balance. Abbreviations : std.diff, standardization difference ; DL, dyslipidemia ; HCM, hypertrophic cardiomyopathy ; DCM, dilated cardiomyopathy ; PVD, peripheral vascular disease ; COPD, chronic obstructive pulmonary disease ; RA, rheumatoid arthritis, PCI, percutaneous coronary intervention. See other abbreviations as in Supplemental Table 1.

Supplemental Table 3.   Baseline characteristics of the study population

| | *Non-Matching* | | | | *Matching* | | |
| | All | Loop only | Loop + β | Std.diff | Loop Only | Loop + β | Std.diff |
	(n = 19,495)	(n = 14,934)	(n = 4,561)		(n = 4,496)	(n = 4,496)	
Age	82 ± 11	82 ± 11	80 ± 11	21.0	80 ± 11	80 ± 11	3.7
Male (%)	49.5	49.8	48.6	2.4	47.5	48.6	-2.4
BMI	22.1 ± 4.7	22.1 ± 4.8	22.3 ± 4.4	-5.0	22.2 ± 4.4	22.3 ± 4.3	-1.8
Smoking (%)	26.8	26.3	28.2	-4.3	27.9	28.1	-0.4
NYHA I	14.4	14.9	12.6	6.8	12.7	12.7	0.1
II	23.0	22.8	23.4	-1.5	23.5	23.3	0.5
III	30.2	29.6	32.1	-5.5	32.3	32.1	0.4
IV	32.5	32.7	31.9	1.8	31.5	31.9	-0.9
Comrbidities (%)							
HT	40.5	39.4	44.2	-9.8	44.5	43.8	1.4
DM	24.5	25.2	22.4	6.6	22.8	22.6	0.5
DL	13.1	12.6	14.9	-6.8	14.7	14.5	0.6
Stroke	9.3	9.3	9.1	1.0	8.8	9.1	-1.1
Af/AFL	32.7	26.0	54.8	-61.3	54.0	54.1	-0.2
MI	9.3	9.6	8.1	5.6	8.1	8.1	-0.3
HCM	1.5	1.5	1.5	0.2	2.0	1.5	3.9
DCM	1.0	0.8	1.6	-7.4	1.3	1.5	-2.4
Amyroid	0.1	0.1	0.0	5.1	0.1	0.0	3.5
Sarcoid	0.2	0.1	0.2	-1.0	0.1	0.2	-2.5
PVD	3.4	3.4	3.4	0.2	3.2	3.4	-1.2
CKD	18.4	19.5	14.8	12.7	15.6	14.9	1.9
Hemodialysis	4.4	4.5	4.1	2.2	4.0	4.0	0.0
Liver failure	0.2	0.1	0.2	-2.2	0.2	0.1	0.8
COPD	8.2	8.3	8.0	1.0	7.7	8.1	-1.6
Cancer	12.0	12.1	11.5	1.7	10.9	11.5	-2.0
RA	1.6	1.6	1.6	0.3	1.3	1.5	-2.0
Dementia	7.4	7.8	6.1	6.8	6.3	6.2	0.6
Treatment (%)							
Cathechoramines	14.4	14.1	15.5	-4.1	15.6	15.2	1.2
IABP	0.6	0.6	0.9	-4.1	0.7	0.9	-1.8
PCPS	0.2	0.2	0.1	1.3	0.1	0.1	-0.6
PCI	2.7	2.5	3.3	-5.1	3.3	3.1	1.4

See abbreviations as in Supplemental Table 1 and Table 1.

Supplemental Table 4.   Baseline characteristics of the study population

| | Non-Matching | | | | Matching | | |
| | All | Loop only | Loop + MRA | Std.diff | Loop Only | Loop + MRA | Std.diff |
	(n=24,412)	(n=14,934)	(n=9,478)		(n=9,330)	(n=9,330)	
Age	82 ± 11	82 ± 11	81 ± 12	7.1	82 ± 11	81 ± 11	2.8
Male (%)	48.8	49.8	47.2	5.1	47.0	47.4	-0.6
BMI	22.0 ± 4.7	22.1 ± 4.8	21.8 ± 4.4	6.5	21.8 ± 4.3	21.8 ± 4.4	-0.7
Smoking (%)	25.8	26.3	25.1	2.7	24.5	25.2	-1.6
NYHA I	14.0	14.9	12.5	7.0	12.7	12.6	0.2
II	23.1	22.8	23.6	-1.9	23.7	23.7	0.0
III	31.0	29.6	33.2	-7.8	32.8	32.8	0.0
IV	31.9	32.7	30.7	4.3	30.8	30.9	-0.2
Comrbidities (%)							
HT	40.6	39.4	42.5	-6.5	42.0	42.2	-0.3
DM	24.0	25.2	22.2	7.0	22.0	22.3	-0.7
DL	13.5	12.6	14.9	-6.8	14.3	14.6	-0.8
Stroke	9.3	9.3	9.2	0.4	9.6	9.3	1.2
Af/AFL	28.8	26.0	33.2	-15.9	32.4	32.7	-0.7
MI	9.7	9.6	9.9	-0.8	9.7	9.8	-0.4
HCM	2.0	1.5	2.8	-9.3	1.6	2.8	-7.9
DCM	0.9	0.8	1.0	-1.8	1.0	1.0	0.1
Amyroid	0.1	0.1	0.1	0.3	0.2	0.1	1.6
Sarcoid	0.2	0.1	0.2	-1.9	0.1	0.2	-2.1
PVD	3.5	3.4	3.6	-0.7	3.5	3.5	-0.2
CKD	15.4	19.5	8.8	31.2	8.8	8.9	-0.4
Hemodialysis	3.0	4.5	0.7	23.8	0.6	0.7	-1.3
Liver failure	0.2	0.1	0.3	-4.3	0.2	0.2	<0.1
COPD	8.3	8.3	8.4	-0.2	8.4	8.4	0.2
Cancer	12.1	12.1	12.1	-0.1	11.9	12.2	-0.9
RA	1.6	1.6	1.7	-0.7	1.6	1.7	-0.5
Dementia	8.1	7.8	8.6	-2.7	8.6	8.6	0.0
Treatment (%)							
Cathechoramines	14.3	14.1	14.6	-1.3	14.3	14.3	-0.1
IABP	0.6	0.6	0.8	-2.6	0.6	0.6	0.1
PCPS	0.2	0.2	0.1	1.0	0.1	0.1	-0.8
Resp	18.7	19.7	17.1	6.9	16.9	17.2	-0.7
PCI	2.8	2.5	3.3	-5.1	2.9	2.9	-0.3

See abbreviations as in Supplemental Table 1 and Table 1.