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ORIGINAL ARTICLE

Discharge use of angiotensin receptor blockers provides comparable effects with angiotensin-converting enzyme inhibitors on outcomes in patients hospitalized for heart failure

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Large-scale, placebo-controlled, randomized clinical trials have shown that angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) reduce mortality and hospitalization in patients with heart failure (HF) caused by left ventricular systolic dysfunction (LVSD). However, it is unknown whether ACE inhibitors and ARBs have similar effects on the long-term outcomes in HF patients encountered in routine clinical practice. The Japanese Cardiac Registry of Heart Failure in Cardiology enrolled HF patients hospitalized with worsening symptoms and they were followed during an average of 2.2 years. The outcome data were compared in patients with LVSD by echocardiography (ejection fraction, EF <40%) according to the predischarge use of ACE inhibitors (n=356) or ARBs (n=372). The clinical characteristics were similar between patients with ACE inhibitor and ARB use, except for higher prevalence of hypertensive etiology and diabetes mellitus. There was no significant difference between ACE inhibitor and ARB use in all-cause death (adjusted hazard ratio 0.958, 95% confidence interval 0.601–1.527, P=0.858) and rehospitalization (adjusted hazard ratio 0.964, 95% confidence interval 0.683–1.362, P=0.836). The effects of ACE inhibitor and ARB use on the outcomes were generally consistent across all clinically relevant subgroups examined, including age, sex, etiology, EF, hypertension, diabetes mellitus, and β-blocker use. Discharge use of ARBs provided comparable effects with ACE inhibitors on outcomes in patients hospitalized for HF. These findings provide further support for guideline recommendations that ARBs can be used in patients with HF and LVSD as an alternative of ACE inhibitors.
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Keywords: ACE inhibitor; ARB; heart failure; outcome; survival

INTRODUCTION

Heart failure (HF) is a leading cause of morbidity and mortality in industrialized countries and is also a growing public health problem, mainly because of aging of the population and the increase in the prevalence of HF in the elderly. Large-scale, placebo-controlled, randomized clinical trials such as CONSENSUS and SOLVD have shown that angiotensin-converting enzyme (ACE) inhibitors significantly improved clinical outcomes in patients with chronic HF with left ventricular systolic dysfunction (LVSD).[1,2]

Angiotensin receptor blockers (ARBs) can directly block angiotensin II at the AT_1 receptor with no accumulation of bradykinin. They should provide similar benefits to ACE inhibitors in blocking the harmful effects of angiotensin II with fewer side effects. ARBs are highly effective in reducing blood pressure (BP) and preventing cardiovascular events in patients with hypertension. They are generally considered to be appropriate specifically in hypertensive patients with cardiovascular diseases including HF. In the ELITE II study, losartan was not superior to captopril in improving survival in elderly HF patients, but was significantly better tolerated.[3] However, ELITE II study was designed as a superiority trial and not to address equivalence between losartan and captopril and thus could not provide any direct information in the difference in efficacy between these two drugs. In the CHARM-alternative study, candesartan reduced the risk of cardiovascular death or hospital admission for HF in patients with LVSD not currently treated with an ACE inhibitor because of earlier intolerance.[4] On the basis of these results, recent treatment guidelines for HF in the United States and Europe recommended that ACE inhibitors should remain the treatment of the first choice in HF, and

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ARB can be a useful alternative agent in a limited group of patients in whom ACE inhibitors are not tolerated.[5,6] Therefore, it still remains to be uncertain whether ARBs are a fully effective substitute for ACE inhibitors in HF. Moreover, it has not been determined whether ACE inhibitors and ARBs have similar effects on the long-term survival in HF patients encountered in routine clinical practice. It should be confirmed in another setting whether there is a benefit associated with ARB use in an unselected population of patients with HF.

The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) is designed to study prospectively the characteristics, treatments, and outcomes in a broad sample of patients hospitalized with HF at teaching hospitals in Japan between January 2004 and June 2005 and the outcomes, including death and hospitalization because of HF, were followed through 2007.[7] The JCARE-CARD program enrolled 2675 patients admitted with HF in a web-based registry with an average follow-up of 2.2 years.

Table 1 Patient characteristics

	All (n=*728*)	*ACE inhibitor* (n=*356*)	*ARB* (n=*372*)	P-*value*
Demographic				
Age (years)	65.9 ± 13.8	65.6 ± 13.9	66.2 ± 13.7	0.622
Older than 65 years (%)	59.2	56.5	61.8	0.141
Male (%)	73.1	76.1	70.2	0.070
Cause of HF (%)				
Ischemic	39.3	38.2	40.3	0.558
Hypertensive	21.2	16.9	25.3	0.005
Cardiomyopathic	38.7	41.9	35.8	0.091
Undetermined	13.5	15.2	11.8	0.187
History				
Hypertension (%)	50.3	46.7	53.6	0.064
Diabetes mellitus (%)	32.3	28.4	36.1	0.026
Hyperlipidemia (%)	30.1	30.4	29.8	0.864
Chronic renal failure (%)	7.0	5.6	8.4	0.151
Serum creatinine (mg per 100 ml)	1.25 ± 1.20	1.14 ± 0.65	1.35 ± 1.54	0.041
Hyperuricemia (%)	50.3	50.7	49.9	0.817
Stroke (%)	13.3	14.2	12.4	0.483
Anemia (%)	10.6	10.5	10.8	0.895
Hemoglobin (g per 100 ml)	13.0 ± 2.3	12.9 ± 2.3	13.1 ± 2.3	0.403
COPD (%)	5.7	4.8	6.6	0.310
Atrial fibrillation (%)	23.6	25.9	21.4	0.148
Sustained VT/Vf (%)	9.0	8.8	9.1	0.894
PCI (%)	20.9	21.8	20.0	0.559
CABG (%)	11.1	12.6	9.8	0.235
Smoking (%)	46.8	46.0	47.6	0.665
Physical findings				
Body mass index (kg m^{-2})	22.9 ± 4.2	22.5 ± 3.9	22.3 ± 4.5	0.011
Heart rate (bpm)	70.4 ± 11.8	70.7 ± 12.4	70.1 ± 11.3	0.445
Discharge SBP (mm Hg)	112.5 ± 16.7	110.0 ± 15.4	113.9 ± 17.8	0.018
Discharge DBP (mm Hg)	65.9 ± 11.4	65.1 ± 11.1	66.7 ± 11.6	0.063
NYHA class at discharge				
I	36.8	30.9	42.5	
II	57.4	62.9	52.2	0.005
III	5.8	6.2	5.4	
Echocardiographic parameters				
LV EDD (mm)	62.3 ± 9.3	62.5 ± 9.5	62.1 ± 9.1	0.576
LV ESD (mm)	53.7 ± 9.4	53.7 ± 9.7	53.6 ± 9.1	0.902
LVEF (%)	26.9 ± 7.4	26.6 ± 7.5	27.2 ± 7.3	0.283
IVS thickness (mm)	9.7 ± 2.9	9.6 ± 3.3	9.7 ± 2.3	0.909
LV PW (mm)	10.0 ± 2.5	9.8 ± 2.8	10.1 ± 2.1	0.139
Admission plasma BNP (pg ml^{-1})	951.1 ± 991.5	926.3 ± 974.5	974.5 ± 1027.4	0.540
Discharge plasma BNP (pg ml^{-1})	352.7 ± 495.8	359.9 ± 541.6	345.2 ± 441.4	0.761

Abbreviations: BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; EDD, end-diastolic dimension; ESD, end-systolic dimension; HF, heart failure; IVS, inter-ventricular septum; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PW, posterior wall; SBP, systolic blood pressure; VT/Vf, ventricular tachycardia/fibrillation.

This study was aimed to investigate the hypothesis that the long-term outcomes, including all-cause mortality and hospitalization because of the worsening of HF, were comparable between ACE inhibitor and ARB use at discharge among a nonselected population of patients hospitalized for HF and LVSD.

METHODS

Patients

The details of the JCARE-CARD program have been described earlier.[7–11] Briefly, eligible patients were those hospitalized with worsening HF as the primary cause of admission. JCARE-CARD enrolled a total of 2675 patients hospitalized for HF at 164 participating hospitals. The diagnosis of HF was established by the simultaneous presence of at least two major criteria or one major criterion in conjunction with two minor criteria by use of the Framingham criteria. Left ventricular ejection fraction (LVEF) was assessed in 1692 patients, and 728 were determined to have LVSD who had documented LVEF $<40\%$ by echocardiography and without valvular etiology. Mean postdischarge follow-up within this group was 801 ± 300 days (2.2 ± 0.8 years).

Data collection and processing

For each patient, baseline data recorded on the form included (1) demography, (2) causes of HF, (3) precipitating causes, (4) comorbidities, (5) complications, (6) clinical status, (7) electrocardiographic and echocardiographic findings, (8) plasma B-type natriuretic peptide, and (9) treatments including discharge medications.

The status of all patients was surveyed after discharge and the following information was obtained: (1) survival, (2) cause of death, and (3) the hospital readmission because of an exacerbation of HF that required more than continuation of their usual therapy on prior admission.

Table 2 Medication use other than ACE inhibitors and ARBs

	All (n=*728*)	*ACE inhibitor* (n=*356*)	*ARB* (n=*372*)	P-*value*
β-blocker	68.3	69.4	67.2	0.528
Diuretics	88.5	88.8	88.2	0.803
Spironolactone	48.5	47.8	49.2	0.697
Digitalis	29.5	32.0	27.2	0.150
Calcium-channel blocker	15.1	13.5	16.7	0.231
Antiarrhythmic	20.5	22.5	18.5	0.190
Aspirin	49.2	47.8	50.5	0.452
Warfarin	44.0	48.3	39.8	0.020
Statin	24.6	26.1	23.1	0.347

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Statistical analysis

Patient characteristics and treatments were compared using Pearson χ^2 test for categorical variables and unpaired *t*-test for continuous variables. Only patients who survived the initial hospitalization were included in the follow-up analysis. The relationship between medication use at discharge and outcomes was evaluated among patients with multivariable adjustment. Baseline clinical variables and treatment factors including other HF medications as shown in Tables 1 and 2 were used in developing the two postdischarge Cox proportional hazards models. A *P*-value of 0.05 was used for criteria for variables to stay in the model. SPSS version 14.0 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

RESULTS

Patient characteristics

Table 1 provides a comparison of clinical characteristics for the entire cohort (*n*=728) and according to the treatment groups: ACE inhibitor (*n*=356) and ARB (*n*=372) use at the time of hospital discharge. The mean age was 66 ± 14 years and 73% were male. HF etiology was ischemic in 39%, cardiomyopathic in 39%, and hypertensive in 21% of the patients. The mean LVEF was 27%. The majority of patients taking ACE inhibitors had enalapril (66%) and some had other ACE inhibitors including temocapril (10%), imidapril (7%), and others. ARBs included candesartan (38%), valsartan (30%), losartan (22%), and others.

The characteristics were similar between patients with ACE inhibitor and ARB use except for higher prevalence of hypertensive etiology and diabetes mellitus in ARB use (Table 1). Serum creatinine, body mass index, and systolic BP were significantly higher in patients with ARB. New York Heart Association functional class was lower in ARB group. However, echocardiographic findings including left ventricular diameters and ejection fraction as well as plasma B-type natriuretic peptide levels did not differ between ACE inhibitor and ARB. Importantly, concurrent cardiovascular medications other than ACE inhibitors or ARBs were similar between groups except for higher use of warfarin in ACE-inhibitor group (Table 2). Clinical characteristics were comparable among different ARB subgroups except for higher prevalence of hypertension, high BP values, and greater wall thickness by echocardiography in patients treated with valsartan or other ARBs (Supplementary Table 1). Medication use was also comparable among different ARB subgroups except for higher use of calcium channel blocker in patients with valsartan or others, which might be due to higher prevalence of hypertension in these groups (Supplementary Table 2).

Postdischarge long-term outcomes

The long-term follow-up data could be obtained in 652 (322 and 330 for ACE inhibitors and ARBs, respectively) out of 728 registered patients (90.0%). Mean postdischarge follow-up was 801 ± 300 days

Table 3 Unadjusted and adjusted hazard risk of long-term outcomes for patients with ACE inhibitors *vs.* ARBs

	Number (%)			
Outcomes	*ACE inhibitors* (n=*322*)	*ARBs* (n=*330*)	*Unadjusted HR (95% CI)*	*Adjusted HR*[a] *(95% CI)*
All cause death	51 (15.8%)	51 (15.5%)	0.958 (0.646–1.405) *P*=0.807	0.958 (0.601–1.527) *P*=0.858
Cardiac death	33 (10.2%)	37 (11.2%)	1.071 (0.669–1.713) *P*=0.775	1.186 (0.680–2.067) *P*=0.548
Sudden death	9 (2.8%)	11 (3.3%)	1.180 (0.489–2.848) *P*=0.712	0.770 (0.270–2.199) *P*=0.626
Hospitalization	101 (31.4%)	99 (30.0%)	0.931 (0.705–1.228) *P*=0.612	0.964 (0.683–1.362) *P*=0.836
All cause death or hospitalization	121 (37.6%)	118 (35.8%)	0.924 (0.717–1.191) *P*=0.540	0.951 (0.694–1.302) *P*=0.752

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard risk.
Use of ACE inhibitors was used as a reference against ARBs when the hazard ratios were calculated.
[a]Adjusted for age, sex, body mass index, hypertension, diabetes mellitus, serum creatinine, New York Heart Association class at discharge, systolic blood pressure, and warfarin.

(2.2 ± 0.8 years): 803 ± 281 for ACE inhibitors and 813 ± 286 days for ARBs (P=0.629).

In the overall cohort of patients with HF and LVSD, mortality at 2.2 years after hospital discharge was 15.6%. Rehospitalization during the same follow-up period was 30.7%. In the group of patients discharged on ARBs, there were 51 deaths from any cause (15.5%) compared with 51 (15.8%) in ACE inhibitors (P=0.807) (Table 3). The rate of cardiac death was also comparable between ACE inhibitor and ARB groups (10.2 *vs.* 11.2%; P=0.775). The rate of rehospitalization because of the worsening of HF did not differ between groups (31.4 *vs.* 30.0%; P=0.612). These postdischarge outcomes were comparable among different ARB subgroups (Supplementary Table 3).

Multivariable analysis

The effect of ACE inhibitor and ARB use on long-term (2.2 years) outcomes was tested in risk-adjusted models. After adjustment for multiple variables predictive of postdischarge mortality, there was no significant difference in a Kaplan–Meier plot for all-cause mortality after hospital discharge between ACE inhibitor and ARB (adjusted hazard ratio 0.958, 95% confidence interval 0.601–1.527, P=0.858) (Table 3; Figure 1). For the combined end point of all-cause mortality or hospitalization, ARB use was also associated with comparable risk (adjusted hazard ratio 0.951, 95% confidence interval 0.694–1.302, P=0.752) (Table 3; Figure 1).

In the risk-adjusted model for all-cause mortality, the effects of ACE inhibitor and ARB use were generally consistent across all clinically relevant subgroups examined, including age (<65 *vs.* ⩾65 years), sex (male *vs.* female), etiology (ischemic *vs.* nonishcemic), LVEF (<25 *vs.* ⩾25%), systolic BP (<110 *vs.* ⩾110 mm Hg), diastolic BP (<65 *vs.* ⩾65 mm Hg), hypertension, diabetes, and β-blocker use (Table 4).

DISCUSSION

This study showed that there was no significant difference in outcomes including all-cause mortality, cardiac mortality, and hospitalization because of the worsening of HF between the discharge use of ACE inhibitors and ARBs among patients hospitalized with HF and LVSD during the long-term (2.2 year) follow-up.

Large-scale, placebo-controlled, randomized clinical trials such as CONSENSUS and SOLVD showed that ACE inhibitors significantly improved clinical outcomes in patients with chronic HF with LVSD.[1,2] ARBs can offer an alternative approach to the inhibition of the renin–angiotensin system. CHARM-alternative study analyzed candesartan compared with placebo among patients with HF who were receiving no background ACE-inhibitor treatment.[4] In addition, *post hoc* subgroup analysis of Val-Heft trial in a subset of 366 patients not taking ACE-inhibitor treatment also showed the large reduction in mortality and morbidity with valsartan.[12] On the basis of these results from clinical trials, current HF management guidelines in United

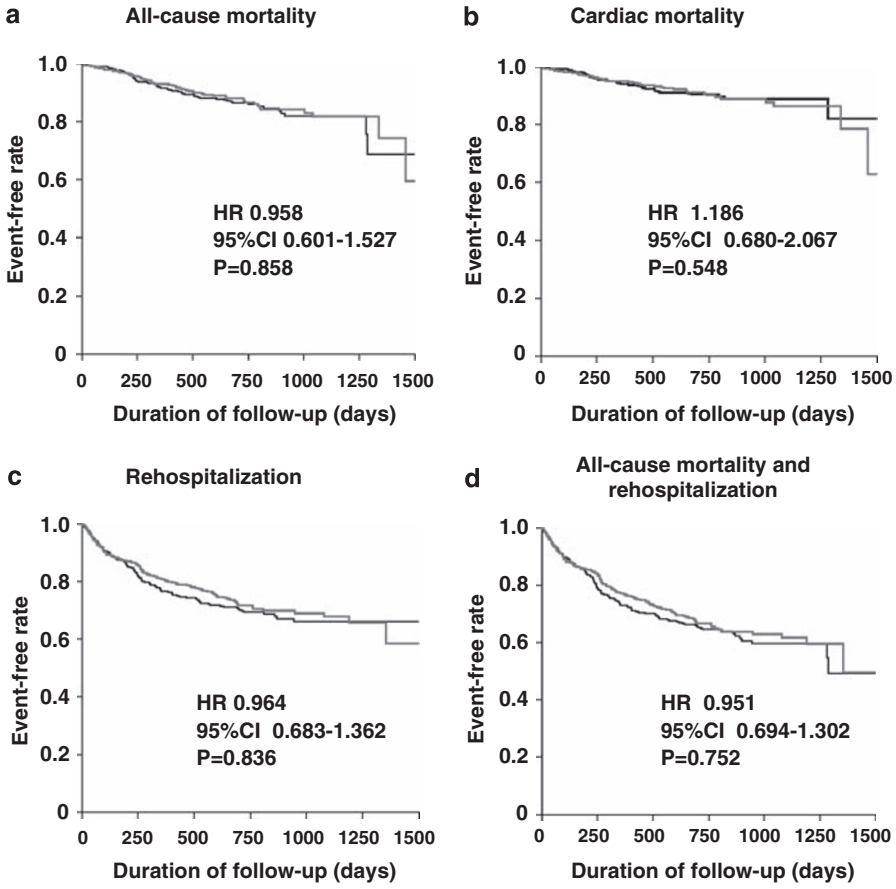

Figure 1 Event-free curves from (**a**) all-cause death, (**b**) cardiac death, (**c**) rehospitalization because of HF, and (**d**) all-cause death or rehospitalization because of HF in patients using ACE inhibitors (black lines; n=322) compared with ARBs (red lines; n=330). The data were adjusted for differences in baseline variables, including age, gender, body mass index, hypertension, diabetes mellitus, serum creatinine level, New York Heart Association class at discharge, systolic blood pressure, and warfarin. A full color version of this figure is available at the *Hypertension Research* journal online.

Table 4 Subgroup analysis of risk-adjusted all-cause death for HF patients with ACE inhibitors *vs.* ARBs

Subgroup	n	*HR for mortality ACE inhibitors vs. ARBs*	*95% CI*	P-*value*
Age				
⩾65 years	386	0.802	0.467–1.378	0.425
<65 years	266	0.871	0.282–2.690	0.810
Gender				
Male	473	0.979	0.573–1.674	0.940
Female	179	0.506	0.165–0.155	0.233
Etiology				
Ischemic	255	0.747	0.397–1.405	0.365
Nonischemic	397	1.024	0.491–2.135	0.950
LVEF				
⩾25%	422	0.825	0.445–1.529	0.541
<25%	230	1.022	0.459–2.275	0.958
Systolic blood pressure at discharge				
⩾110 mm Hg	388	0.756	0.398–1.437	0.394
<110 mm Hg	264	1.003	0.498–2.131	0.937
Diastolic blood pressure at discharge				
⩾65 mm Hg	318	0.556	0.250–1.236	0.150
<65 mm Hg	334	1.156	0.645–2.074	0.626
Hypertension[a]				
Yes	326	0.966	0.422–2.215	0.935
No	322	1.178	0.645–2.150	0.593
Diabetes				
Diabetes	206	1.413	0.590–3.386	0.438
No diabetes	446	0.760	0.417–1.384	0.369
β-blocker				
β-blocker use	446	0.928	0.492–1.748	0.816
No β-blocker use	206	0.757	0.353–1.623	0.475

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; HF, heart failure; HR, hazard risk; LVEF, left ventricular ejection fraction.
Use of ACE inhibitors was used as a reference against ARBs when the hazard ratios were calculated.
[a]Four subjects with insufficient information are not included in the analysis.

States, Europe, and Japan have recommend that ACE inhibitors should remain the treatment of the first choice in HF with LVSD. In patients in whom ACE inhibitors are not tolerated, an ARB might be a useful alternative agent to block the renin—angiotensin–aldosterone system.[5,6]

The ELITE II study showed that losartan was not superior to captopril in improving survival in elderly HF patients.[3] Therefore, this study has extended the results shown by ELITE II, which, however, was a superiority trial and was not designed to address equivalence between losartan and captopril and thus could not provide any direct information in the difference in efficacy between these two drugs. Moreover, both CHARM and Val-Heft have suggested that ARBs may have similar beneficial effects on outcomes as ACE inhibitors in patients with HF.[4,12] However, these trials used placebo, not ACE inhibitors, as a comparator. Therefore, this study provided the first demonstration that ARBs could exert comparable effects with ACE inhibitors on outcomes in HF patients. The survival curves of ACE inhibitors and ARBs were almost completely overlapped during the average follow-up of 2.2 years (Figure 1). These findings should reassure clinicians that ARB is as effective as ACE inhibitors, and provides a similar opportunity to improve outcomes for patients with HF as ACE inhibitors. Moreover, our results parallel the findings of OPTIMAAL and VALIANT, which established the noninferiority of ARBs as compared with captopril in patients with LVSD or HF after acute myocardial infarction.[13,14]

Although evidence from randomized clinical trials shows a significant survival benefit for ARB therapy in systolic HF,[3,4,15,16] such trials are recognized as unrepresentative of the general HF population encountered in routine clinical practice. Therefore, uncertainty pertaining to the applicability of these findings to the population of patients with HF at large persists. Therefore, it is of critical importance to analyze the registry data of HF patients. For this purpose, JCARE-CARD was designed to focus on the demographic and clinical characteristics, treatment strategies, and outcomes in HF patients in Japan.[7] The results from representative HF population in JCARE-CARD extended the results of ELITE II conducted in selected outpatients with systolic HF to a diverse cohort of patients with HF and confirmed the findings from large-scale clinical trials in that ARB treatment could be associated with survival benefit to the same extent as ACE inhibitors. Therefore, ARBs, one of major classes of antihypertensive drugs, are useful in reducing adverse events not only in hypertensive patients, but also in those with HF.

Most patients with HF have hypertension.[17] Hypertension is not only an important comorbidity of HF, but it also contributes to the pathogenesis of systolic and diastolic HF by inducing cardiac hypertrophy. In addition, hypertension is a major risk factor for ischemic heart disease and can lead to the development of HF through impaired cardiac contractility, remodeling, and eventual systolic and diastolic dysfunction.[18] Target BP values in HF have not been firmly established, but, in most successful clinical trials, systolic BP was lowered to the range of 110 to 130 mm Hg.[19] On this basis, the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention have made the recommendation that the target BP in patients with HF should be $<130/80$ mm Hg, and also suggest that consideration should be given to lowering the BP even further to $<120/80$ mm Hg.[20] This study showed that the comparable effects of ACE inhibitors and ARBs on the long-term outcomes were consistent irrespective of the BP levels (Table 4).

Several crucial limitations inherent in the design of this study should be considered. First, documentation of ACE inhibitor or ARB prescription at hospital discharge might not accurately reflect the level of drug use after discharge or adherence to ACE inhibitor or ARB use over time. Second, JCARE-CARD is not a prospective randomized trial and, despite covariate adjustment, other measured and unmeasured factors might have influenced outcomes. We thus could not completely exclude other unmeasured factors that might also affect outcomes. Third, the number of the study patients was not sufficient to avoid type 2 (beta) statistical error in this study. Fourth, as the dose of medication was not recorded, this study could not confirm that ACE inhibitors and ARBs exerted comparable inhibitory effects against angiotensin II in the studied patients. Finally, data were dependent on the accuracy of documentation and abstraction by individual medical centers that participated in the program. However, it was not the objective of this survey to restrict enrollment to the narrowly defined population of HF patients usually included in clinical trials, but rather to include a broad range of patients reflecting the current reality of clinical practice rather than trials.

In conclusion, discharge use of ARBs provided comparable effects with ACE inhibitors on outcomes in patients hospitalized for HF in routine clinical practice. These findings provide further support for guideline recommendations that ARBs can be used in patients with HF and LVSD as an alternative of ACE inhibitors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)