

The use of angiotensin II receptor blocker is associated with greater recovery of cardiac function than angiotensin-converting enzyme inhibitor in dilated cardiomyopathy

Nobuyuki Enzan¹, Shouji Matsushima^{1*}, Tomomi Ide¹, Takeshi Tohyama², Kouta Funakoshi², Taiki Higo³ and Hiroyuki Tsutsui¹

¹Department of Cardiovascular Medicine, Faculty of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka, 812-8582, Japan; ²Center for Clinical and Translational Research, Kyushu University Hospital, Fukuoka, Japan; and ³Department of Cardiovascular Medicine, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan

Abstract

Aims Angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) have been shown to be associated with recovery of cardiac function in patients with dilated cardiomyopathy (DCM). The aim of this study was to assess comparative effectiveness of ACEis vs. ARBs on recovery of left ventricular ejection fraction (LVEF) among patients with DCM.

Methods and results We analysed the clinical personal records of DCM, a national database of the Japanese Ministry of Health, Labour and Welfare, from 2003 to 2014. Patients with LVEF < 40% and on either ACEis or ARBs were included. Eligible patients were divided into two groups according to the use of ACEis or ARBs. A one-to-one propensity case-matched analysis was used. The primary outcome was defined as LVEF ≥ 40% at 3 years of follow-up. Out of 4618 eligible patients, 2238 patients received ACEis and 2380 patients received ARBs. Propensity score matching yielded 1341 pairs. Mean age was 56.0 years, 2041 (76.1%) were male, median duration of heart failure was 1 year, and mean LVEF was 27.6%. The primary outcome was observed more frequently in ARB group than in ACEi group (59.8% vs. 54.1%; odds ratio 1.26; 95% confidence interval 1.08–1.47; $P = 0.003$). The per-protocol analysis showed similar results (62.0% vs. 54.0%; odds ratio 1.39; 95% confidence interval 1.17–1.66; $P < 0.001$). The change in LVEF from baseline to 3 years of follow-up was greater in ARB group than in ACEi group ($15.8 \pm 0.4\%$ vs. $14.0 \pm 0.4\%$, $P = 0.003$). The subgroup analysis showed that this effect was observed independently of systolic blood pressure, heart rate, LVEF, chronic kidney disease, and concomitant use of beta-blockers and mineralocorticoid receptor antagonists.

Conclusions The use of ARBs was associated with LVEF recovery more frequently than ACEis among patients with DCM and reduced LVEF.

Keywords Dilated cardiomyopathy; Heart failure with reduced ejection fraction; Angiotensin-converting enzyme inhibitor; Angiotensin II receptor blocker

Received: 12 July 2021; Revised: 6 November 2021; Accepted: 14 December 2021

*Correspondence to: Shouji Matsushima, Department of Cardiovascular Medicine, Faculty of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan. Tel: (+81)92-642-5360; Fax: (+81)92-642-5374. Email: matsushima.shoji.056@m.kyushu-u.ac.jp

Introduction

Angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) have an established role

as the first-line treatment for a number of cardiovascular diseases. In particular, ACEis have been shown to reduce mortality in patients with heart failure (HF) with reduced ejection fraction (HFrEF).^{1,2} ARBs are also reported to reduce

cardiovascular mortality and morbidity in patients with symptomatic HF.^{3,4} In the PARADIGM-HF trial, angiotensin receptor neprilysin inhibitor (ARNI) has shown better cardiovascular protective effects in patients with HF than enalapril.⁵ Although, in the latest European Society of Cardiology (ESC) guideline, ACEis or ARBs are recommended to be replaced by ARNI in ambulatory patients with HFrEF, who remain symptomatic despite optimal treatment,⁶ ACEis and ARBs are still main drugs used for HFrEF.

ELITE II study and a randomized controlled study regarding valsartan and losartan demonstrated that ARBs were not superior to ACEis in improving survival in HF patients, but were significantly better tolerated than ACEis.^{7,8} Accordingly, the 2013 American College of Cardiology/American Heart Association guidelines and 2016 ESC HF guidelines recommend that ARBs are appropriate in patients intolerant of ACEis.^{9,10} However, in ELITE study, ARB losartan reduced a mortality in elder HF patients compared with ACEi captopril.¹¹ A propensity-matched study evaluating long-term prognosis (≥ 8 years) in elder HF patients on ACEis or ARBs showed that ARBs were associated with reduced mortality and a trend for reduced HF hospitalization,¹² raising a possibility that ARBs could provide better prognosis than ACEis in the long run.

Dilated cardiomyopathy (DCM) is a non-ischaemic heart muscle disease with structural and functional myocardial abnormalities. The clinical feature of DCM is left or biventricular dilatation and systolic dysfunction in the absence of coronary artery disease, hypertension, valvular disease, or congenital heart disease.¹³ In particular, DCM with reduced ejection fraction (EF) has a poor prognosis than those with preserved EF.¹⁴ DCM is a major cause of HF in the world.¹⁵ Therefore, a better therapeutic strategy for DCM needs to be established.

A non-negligible number of patients with HFrEF experience left ventricular EF (LVEF) recovery as a result of advances in drug therapy, devices, and coronary revascularization.¹⁶ Patients with LVEF $\geq 40\%$ who previously had LVEF $< 40\%$ were defined as HF with recovered EF (HF-REF).¹⁷ Several studies have reported that HF-REF has better prognosis than HFrEF and HF with preserved EF (HFpEF).^{18–22} Thus, the recovery of LVEF is often used as a surrogate endpoint in HF clinical trials.^{23,24} Renin–angiotensin–aldosterone system (RAAS) inhibitors are known to be associated with HF-REF. The Val-HeFT echocardiographic substudy demonstrated that valsartan, one of ARBs, reversed LV remodelling.²⁵ Recently, we have shown that the use of ACEis or ARBs is associated with recovery of LVEF in patients with DCM.²⁶

There are differences in pharmacological action between ACEis and ARBs. ACEi blocks RAAS by inhibiting angiotensin-converting enzyme (ACE) activity but induces ACE-independent chymase-mediated production of angiotensin II and aldosterone.^{27,28} On the other hand, ARBs inhibit RAAS by the direct blockade of angiotensin II receptor. Activation of RAAS plays a pivotal role in development of LV remodelling. To date, the effect of ACEis and ARBs has been

investigated in HF patients with ischaemic aetiology.^{8,29} Non-ischaemic cardiomyopathy is known to experience recovery of LVEF more frequently than ischaemic cardiomyopathy.^{30,31} However, it has not been fully elucidated whether ACEis and ARBs have similar or different effects on recovery of cardiac dysfunction in patients with DCM.

The clinical personal record is a nationwide administrative database of public expenditure for refractory disease maintained by the Japanese Ministry of Health, Labour and Welfare to register and certificate intractable diseases, including cardiomyopathies, throughout Japan. This database is useful to investigate clinical features and routine practice in DCM patients in Japan.³² The aim of this study was to examine whether ARBs and ACEis could be superior to the other in terms of recovery of LVEF among DCM patients with reduced LVEF by analysing a nationwide database of the clinical personal record.

Methods

Clinical personal record

The clinical personal record, a nationwide administrative database of public expenditure for refractory disease by the Japanese Ministry of Health, Labour and Welfare, has been established to register and certificate intractable diseases, including cardiomyopathies, throughout Japan.³² This record prospectively and annually collected the following data: (i) demographic data [age, sex, duration of HF, and New York Heart Association (NYHA) functional class]; (ii) vital signs; (iii) co-morbidities; (iv) electrocardiographic data; (v) echocardiographic data; (vi) laboratory data; and (vii) medication use. This database does not collect information about clinical outcomes such as hospitalization and death. DCM was diagnosed on a dilated LV and reduced LVEF in the absence of any specific cardiac or systemic diseases such as hypertensive heart disease, valvular heart disease, congenital heart disease, coronary artery disease, alcoholic cardiomyopathy, cardiomyopathy caused by toxins/medications, amyloidosis, sarcoidosis, connective tissue disease, dystrophy, or metabolic disease such as Pompe disease or Fabry disease. The data in this registry were collected from any types of hospitals in Japan. All clinical personal records were registered after being reviewed by certified cardiologists. The present study employed this nationwide database from 2003 to 2014.

Patient selection

Patients older than 18 years old with LVEF $< 40\%$ were identified from the clinical personal record of DCM described earlier. Screened patients were excluded from enrolment if they

received both ACEis and ARBs, neither ACEis nor ARBs, left ventricular assist device, or heart transplantation during the follow-up period or they were not assessed with echocardiography at 3 years of follow-up. The eligible patients were divided into two groups according to the use of ACEis or ARBs. All patients had any prior symptoms or signs of HF, including dyspnoea, palpitation, chest pain, oedema, and hepatomegaly.

Outcomes

The primary outcome was defined as an LVEF $\geq 40\%$ at 3 years of follow-up, known as HF-REF. Secondary outcomes were a decrease in left ventricular diastolic diameter (LVDd) $\geq 10\%$ and a decrease in LV systolic diameter (LVDs) $\geq 10\%$. Echocardiographic data were assessed in each participating hospital. Factors associated with an increase in LVEF, including changes in systolic blood pressure, diastolic blood pressure, heart rate, and use of beta-blockers and digitalis at 3 years of follow-up, were investigated. We also assessed the primary outcome among subgroups: age (≥ 60 vs. < 60 years old), sex, systolic blood pressure (≥ 120 vs. < 120 mmHg), heart rate (≥ 80 vs. < 80 b.p.m.), NYHA functional class (I–II vs. III–IV), LVEF (≥ 30 vs. $< 30\%$), atrial fibrillation, anaemia, chronic kidney disease (Stage 1–2 vs. 3–5), and concomitant use of beta-blockers and mineralocorticoid receptor antagonists (MRAs).

Statistical analysis

Patient characteristics were compared with Pearson χ^2 test for categorical variables and Student's *t*-test or Wilcoxon rank-sum test for continuous variables and were presented as mean \pm standard deviation or median with inter-quartile range.

A propensity score was estimated by fitting a logistic regression model, which adjusted for age, sex, duration of HF, NYHA functional class (I–II vs. III–IV), systolic blood pressure, diastolic blood pressure, heart rate, atrial fibrillation, pacing, left bundle branch block, LVEF, hypertension, diabetes mellitus, hyperuricaemia, chronic kidney disease, B-type natriuretic peptide, beta-blockers, MRAs, loop diuretics, thiazides, digitalis, amiodarone, and oral inotropes. A one-to-one pair matching between the two groups was performed by nearest-neighbour matching without replacement. Covariate balances before and after matching were checked by comparison of standardized mean difference (SMD). An SMD < 0.1 was considered to indicate a negligible imbalance between the two groups.

Odds ratio (OR) was estimated by logistic regression model and presented with 95% confidence interval (CI) and *P* value.

The changes in LVEF were compared with the use of analysis of covariance.

The per-protocol population was defined as patients who received ACEis or ARBs consistently throughout follow-up period. A per-protocol analysis was also performed using this per-protocol population.

Considering intra-observer and inter-observer variability of echocardiographic evaluations, increases in LVEF $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ were also evaluated as outcomes. The sensitivity analysis of outcomes by using combination of multiple imputation and inverse probability of treatment weighting was also conducted.³³ For the missing data at baseline, multiple imputation was performed ($n = 10$) by predictive mean matching for continuous variables and logistic regression model for binary variables. A propensity score was estimated by fitting a logistic regression model, which adjusted for all baseline covariates in each dataset. ORs for outcomes were estimated by inverse probability weighting. Estimates from 10 iterations were combined with the use of Rubin's rule. In addition, multivariate logistic regression analysis adjusted for same covariates used in propensity score matching was performed as complete case analysis.

Because the responsiveness to the biventricular pacing could be a possible confounder, patients without biventricular pacing were selected from the eligible patients and the multivariate logistic regression analysis adjusted for same covariates used in propensity score matching was performed. The effectiveness of candesartan, losartan, and valsartan on LVEF recovery to LVEF $\geq 40\%$ was assessed with multivariate analysis including covariates listed earlier.

All tests were two tailed, and $P < 0.05$ was considered to be statistically significant. All analyses were performed with the SAS statistical package (Version 9.4, SAS Institute, Cary, NC). The authors had full access to and take full responsibility for the integrity of the data.

Ethic statements

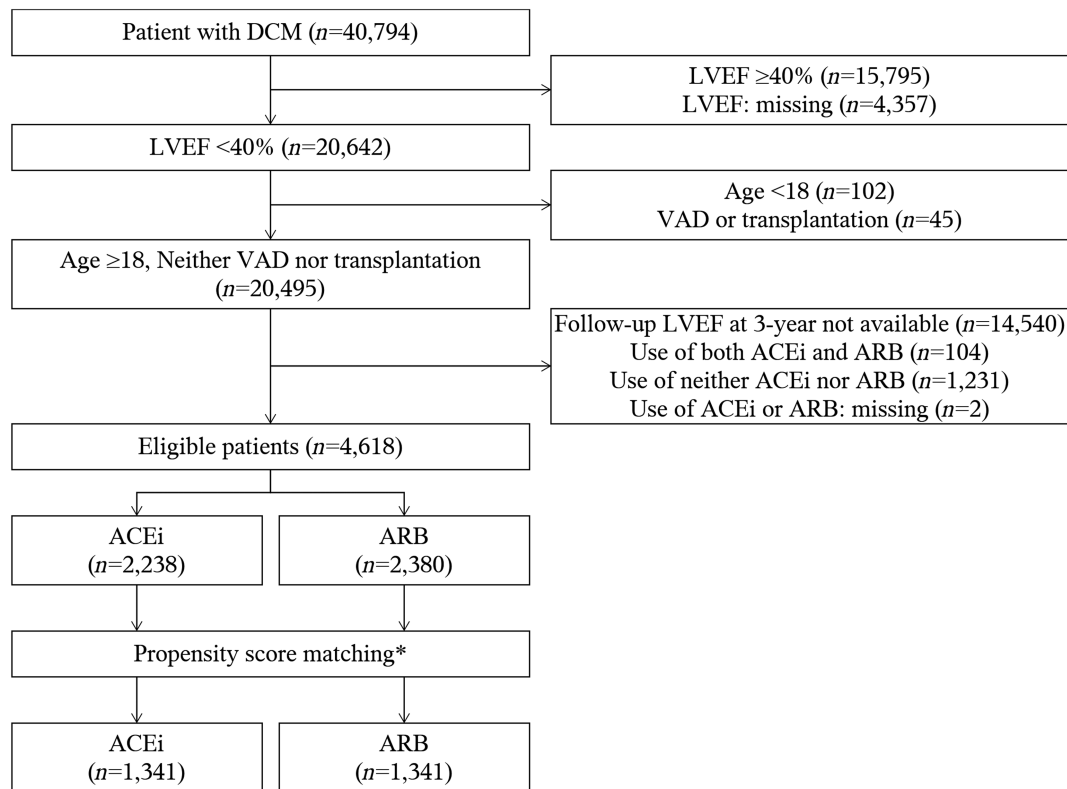
This study protocol was organized to ensure compliance with the Declaration of Helsinki. The original study protocol was approved by the Institutional Review Board at Kyushu University. An 'opt-out' approach was applied to consent because this study analysed a nationwide administrative database.

Results

Patient characteristics

Figure 1 shows the method of patient selection in this study. From 2003 to 2014, 40 794 consecutive patients with DCM were screened and 20 495 patients were identified as HFREF and older than 18 years old. Of them, 14 540 patients who

Figure 1 Patient selection. * Adjusted for age, sex, duration of heart failure, New York Heart Association functional class (I–II vs. III–IV), systolic blood pressure, diastolic blood pressure, heart rate, atrial fibrillation, pacing, left bundle branch block, left ventricular ejection fraction (LVEF), hypertension, diabetes mellitus, hyperuricaemia, chronic kidney disease, BNP, beta-blocker, mineralocorticoid receptor antagonist, loop diuretics, thiazide, digitalis, amiodarone, and oral inotropes. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DCM, dilated cardiomyopathy; VAD, ventricular assist device.



were not assessed with echocardiography at 3 years of follow-up, 104 patients with both ACEis and ARBs, 1231 patients with neither ACEis nor ARBs, and 2 patients whose medication data were missing were excluded. The remaining 4618 patients were finally included in the present analysis, and 2238 patients had ACEis and 2380 had ARBs. Propensity score matching yielded each 1341 patients. Details of ACEis and ARBs are shown in Supporting Information, *Table S1*. Enalapril (64.6%) was most commonly used in the ACEi group, and candesartan (36.1%), losartan (30.2%), and valsartan (22.5%) were mainly used in the ARB group.

Patient characteristics before and after propensity score matching are shown in *Table 1*. After propensity score matching, variables were considered to be well balanced. In matching cohort, mean age was 56.0 years, 2041 (76.1%) were male, and median duration of HF was 1 years. Echocardiography demonstrated that LVEF ($27.7 \pm 7.5\%$ vs. $27.6 \pm 7.4\%$, $P = 0.82$, SMD = 0.009), LVDd (64.6 ± 8.1 vs. 64.3 ± 8.5 mm, $P = 0.33$, SMD = 0.038), LVDs (56.0 ± 8.3 vs. 55.5 ± 9.0 mm, $P = 0.14$, SMD = 0.058), and Grade III–IV of mitral regurgitation (17.7% vs. 14.9%, $P = 0.078$, SMD = 0.076) were comparable between ACEi and ARB groups.

Clinical outcomes

The change in LVEF was greater in ARB group than ACEi group ($15.8 \pm 0.4\%$ vs. $14.0 \pm 0.4\%$, $P = 0.003$) (*Figure 2*). Changes in systolic blood pressure, diastolic blood pressure, and heart rate were comparable between the two groups.

Figure 3 shows primary and secondary outcomes. The prevalence of LVEF recovery at 3 years of follow-up in the ARB group was higher than that in the ACEi group (59.8% vs. 54.1%; OR 1.26; 95% CI 1.08–1.47; $P = 0.003$). While the prevalence of decrease in LVDd $\geq 10\%$ did not differ between the two groups (45.3% vs. 43.5%; OR 1.08; 95% CI 0.92–1.26; $P = 0.34$), the prevalence of decrease in LVDs $\geq 10\%$ tended to be more frequent in the ARB group (60.9% vs. 57.2%; OR 1.17; 95% CI 1.00–1.37; $P = 0.056$).

In the ACEi group, 946 patients (70.6%) continued to receive ACEi at 3 years of follow-up. On the other hand, in the ARB group, 1088 patients (81.3%) continued to receive ARB. Per-protocol analysis consistently showed that ARB increased the prevalence of LVEF recovery (62.0% vs. 54.0%; OR 1.39; 95% CI 1.17–1.66; $P < 0.001$) and decreases in LVDd $\geq 10\%$ (47.1% vs. 42.4%; OR 1.21; 95% CI 1.01–1.45;

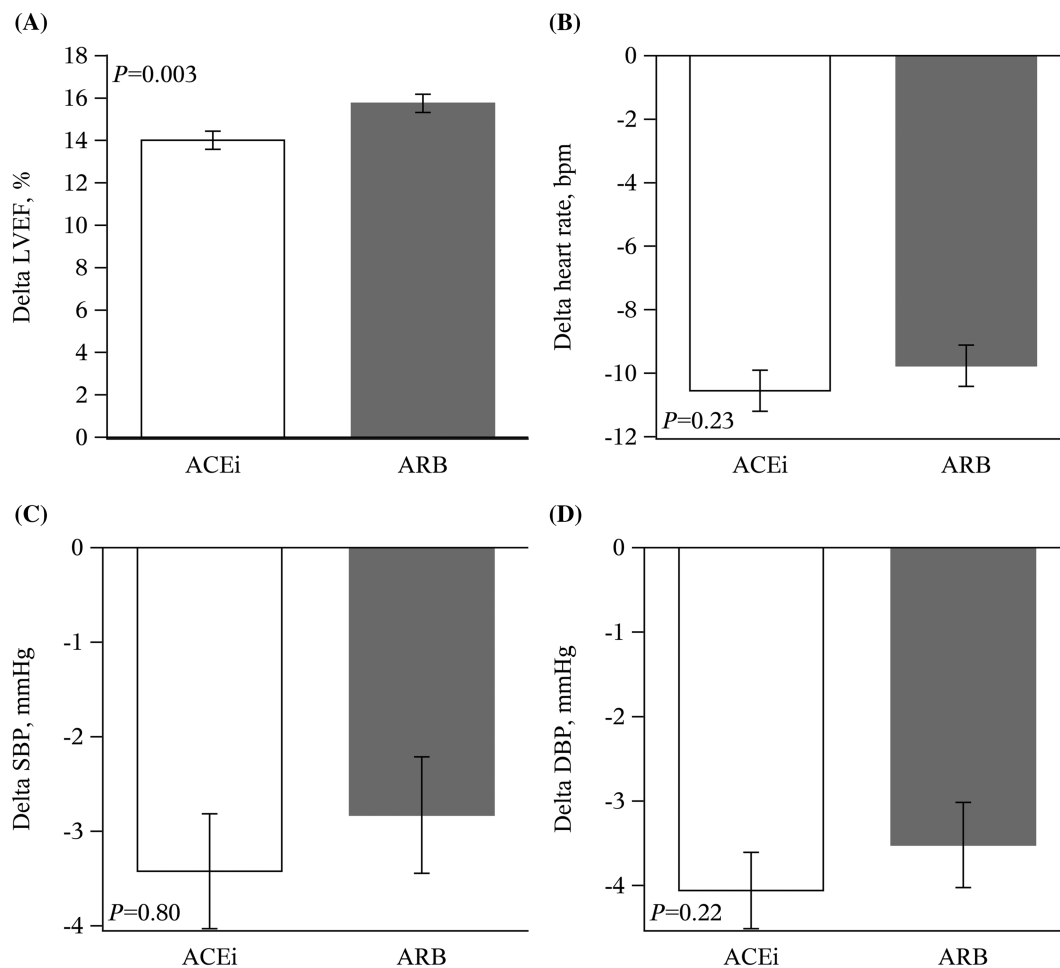
Table 1 Patient characteristics

| Variables | Before propensity score matching | | | After propensity score matching | | | |
|--------------------------------------|----------------------------------|--------------------|---------|---------------------------------|--------------------|-------|---------|
| | ACEI (n = 2238) | ARB (n = 2380) | P value | ACEI (n = 1341) | ARB (n = 1341) | SMD | P value |
| Demographics | | | | | | | |
| Age (years) | 56.0 ± 13.3 | 57.5 ± 12.9 | <0.001 | 55.9 ± 13.3 | 56.2 ± 13.2 | 0.019 | 0.63 |
| Male | 1746 (78.0) | 1800 (75.6) | 0.055 | 1025 (76.4) | 1016 (75.8) | 0.016 | 0.68 |
| Duration of HF (years) | 1.0 (0.0–7.0) | 1.0 (0.0–4.0) | <0.001 | 1.0 (0.0–4.0) | 1.0 (0.0–4.0) | 0.005 | 0.83 |
| NYHA III–IV | 689 (31.9) | 779 (34.1) | 0.12 | 456 (34.0) | 462 (34.5) | 0.009 | 0.81 |
| Vital signs | | | | | | | |
| SBP (mmHg) | 118.9 ± 20.4 | 121.8 ± 22.3 | <0.001 | 119.8 ± 21.4 | 119.4 ± 21.3 | 0.019 | 0.64 |
| DBP (mmHg) | 73.6 ± 15.5 | 75.2 ± 16.9 | <0.001 | 74.3 ± 15.9 | 74.4 ± 16.5 | 0.007 | 0.86 |
| Heart rate (b.p.m.) | 80.4 ± 20.7 | 81.8 ± 21.3 | 0.063 | 82.2 ± 21.4 | 82.1 ± 21.5 | 0.003 | 0.94 |
| Co-morbidities | | | | | | | |
| Hypertension | 164 (7.3) | 287 (12.1) | <0.001 | 119 (8.9) | 125 (9.3) | 0.016 | 0.69 |
| Diabetes mellitus | 62 (2.8) | 66 (2.8) | 1.00 | 34 (2.5) | 33 (2.5) | 0.005 | 0.90 |
| CKD Stage 3–5 | 842 (37.6) | 960 (40.3) | 0.056 | 496 (37.0) | 497 (37.1) | 0.002 | 0.97 |
| Hyperuricaemia | 909 (40.6) | 971 (40.8) | 0.90 | 579 (43.2) | 571 (42.6) | 0.012 | 0.75 |
| Laboratory data | | | | | | | |
| Haemoglobin (g/dL) | 14.2 ± 1.8 | 14.1 ± 1.9 | 0.35 | 14.2 ± 1.8 | 14.2 ± 1.9 | 0.007 | 0.86 |
| Albumin (g/dL) | 4.1 ± 0.5 | 4.1 ± 0.5 | 0.082 | 4.1 ± 0.5 | 4.1 ± 0.5 | 0.034 | 0.45 |
| AST (U/L) | 25.0 (19.0–34.0) | 24.0 (19.0–33.0) | 0.36 | 25.0 (20.0–35.0) | 24.0 (19.0–33.5) | 0.034 | 0.11 |
| ALT (U/L) | 24.0 (16.0–38.0) | 24.0 (16.0–38.0) | 0.85 | 25.0 (17.0–39.0) | 24.0 (17.0–39.0) | 0.011 | 0.45 |
| Creatinine (mg/dL) | 0.90 (0.75–1.06) | 0.90 (0.76–1.09) | 0.17 | 0.90 (0.76–1.07) | 0.90 (0.77–1.07) | 0.072 | 0.60 |
| Uric acid (mg/dL) | 6.9 ± 2.0 | 6.9 ± 2.0 | 0.84 | 7.0 ± 2.1 | 6.9 ± 1.9 | 0.043 | 0.31 |
| Sodium (mEq/L) | 140.3 ± 3.2 | 140.6 ± 3.2 | 0.002 | 140.4 ± 3.2 | 140.6 ± 3.3 | 0.061 | 0.080 |
| BNP (pg/mL) | 234.5 (84.8–597.9) | 260.0 (86.0–669.5) | 0.059 | 252.0 (85.8–639.0) | 252.2 (79.8–650.0) | 0.003 | 0.60 |
| Electrocardiographic findings | | | | | | | |
| Atrial fibrillation | 484 (21.6) | 522 (21.9) | 0.007 | 281 (21.0) | 284 (21.2) | 0.005 | 0.89 |
| Pacing | 62 (2.8) | 64 (2.7) | 0.005 | 40 (3.0) | 40 (3.0) | 0.000 | 1.00 |
| Biventricular pacing | 12 (0.5) | 13 (0.5) | 0.96 | 8 (0.6) | 11 (0.8) | 0.027 | 0.49 |
| Left bundle branch block | 164 (7.3) | 205 (8.6) | 0.047 | 110 (8.2) | 114 (8.5) | 0.011 | 0.78 |
| Echocardiographic findings | | | | | | | |
| LVEF (%) | 27.9 ± 7.5 | 28.3 ± 7.3 | 0.11 | 27.7 ± 7.5 | 27.6 ± 7.4 | 0.009 | 0.82 |
| LVDD (mm) | 64.6 ± 8.3 | 63.8 ± 8.4 | 0.002 | 64.6 ± 8.1 | 64.3 ± 8.5 | 0.038 | 0.33 |
| LVDS (mm) | 55.8 ± 8.6 | 54.9 ± 8.7 | <0.001 | 56.0 ± 8.3 | 55.5 ± 9.0 | 0.058 | 0.14 |
| MR III–IV | 317 (17.4) | 286 (15.1) | 0.062 | 196 (17.7) | 160 (14.9) | 0.076 | 0.078 |
| Medication | | | | | | | |
| Beta-blockers | 1674 (74.8) | 1896 (79.7) | 0.116 | 1076 (80.2) | 1087 (81.1) | 0.021 | 0.59 |
| MRA | 820 (36.6) | 828 (34.8) | 0.039 | 515 (38.4) | 505 (37.7) | 0.015 | 0.69 |
| Loop diuretics | 1741 (78.4) | 1903 (80.6) | 0.063 | 1069 (79.7) | 1070 (79.8) | 0.002 | 0.96 |
| Thiazides | 44 (2.0) | 45 (1.9) | 0.85 | 23 (1.7) | 22 (1.6) | 0.006 | 0.88 |
| Digitalis | 705 (31.5) | 634 (26.6) | <0.001 | 352 (26.2) | 354 (26.4) | 0.003 | 0.93 |
| Amodarone | 268 (12.0) | 274 (11.6) | 0.63 | 174 (13.0) | 172 (12.8) | 0.004 | 0.91 |
| Oral inotropes | 99 (4.4) | 90 (3.8) | 0.032 | 53 (4.0) | 54 (4.0) | 0.004 | 0.92 |

ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BNP, brain-type natriuretic peptide; CKD, chronic kidney disease; DBP, diastolic blood pressure; HF, heart failure; LVDD, left ventricular diastolic diameter; LVDS, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation; SMD, standardized mean difference.

Data are shown as n (%) or means ± SD otherwise specified.

Figure 2 Change in left ventricular ejection fraction and haemodynamics. (A) Delta left ventricular ejection fraction (LVEF), (B) delta heart rate, (C) delta systolic blood pressure (SBP), and (D) delta diastolic blood pressure (DBP). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.



$P = 0.036$) and LVDs $\geq 10\%$ (63.1% vs. 55.0%; OR 1.40; 95% CI 1.16–1.68; $P < 0.001$) (Figure 3).

Sensitivity analyses are shown in Supporting Information, Table S2. The prevalence of increases in LVEF $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ was higher in the ARB group by the propensity score-matched analysis, complete case analysis, and multiple imputation analysis. Combination of multiple imputation and inverse probability of treatment weighting showed that all of the adjusted SMDs derived from imputed dataset were < 0.1 and considered to be well balanced (Supporting Information, Figure S1). The use of ARB was consistently associated with LVEF recovery even in patients without biventricular pacing (Supporting Information, Table S3).

Subgroup analysis showed that ARB increased frequency of LVEF recovery regardless systolic blood pressure, heart rate, LVEF, chronic kidney disease, and concomitant use of beta-blockers and MRAs (Figure 4).

We also analysed the prescription rate of medication at 3 years of follow-up related to cardiac function. The use of

beta-blockers and digitalis did not differ between the two groups (Table 2).

We compared the effects of candesartan, losartan, and valsartan on LVEF recovery to $\geq 40\%$ in ARB group. There is no significant difference between candesartan and losartan (OR 0.92; 95% CI 0.69–1.22; $P = 0.34$) or between candesartan and valsartan (OR 1.09; 95% CI 0.80–1.48; $P = 0.39$).

Discussion

The present study demonstrated that ARBs significantly increased frequency of LVEF recovery compared with ACEis among DCM patients with reduced LVEF. This effect was observed independently of systolic blood pressure, heart rate, LVEF, chronic kidney disease, and concomitant use of beta-blockers and MRAs.

Figure 3 Primary and secondary outcomes. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor II blocker; CI, confidence interval; EF, ejection fraction; ITT, intention-to-treat analysis; LVDD, left ventricular diastolic diameter; LVDS, left ventricular systolic diameter; OR, odds ratio.

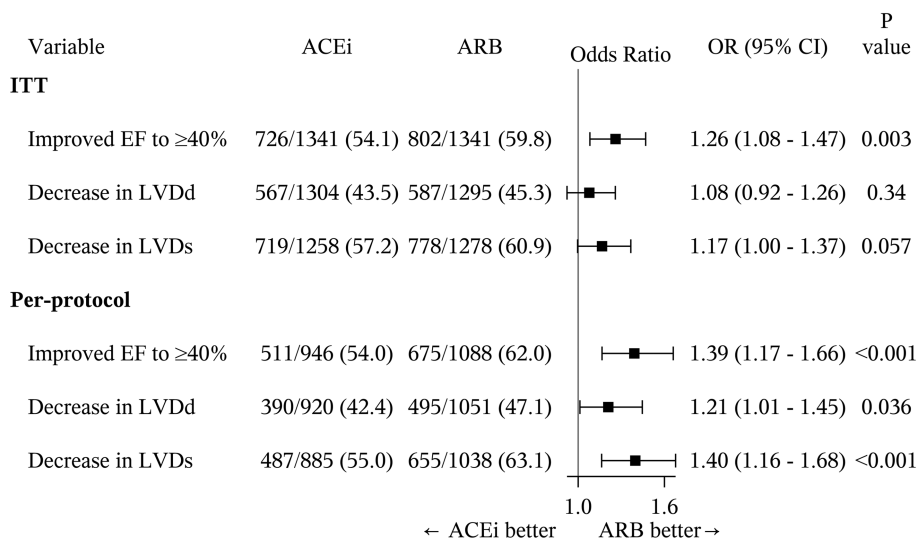


Figure 4 Subgroup analysis. ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor II blocker; CI, confidence interval; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; OR, odds ratio; SBP, systolic blood pressure.

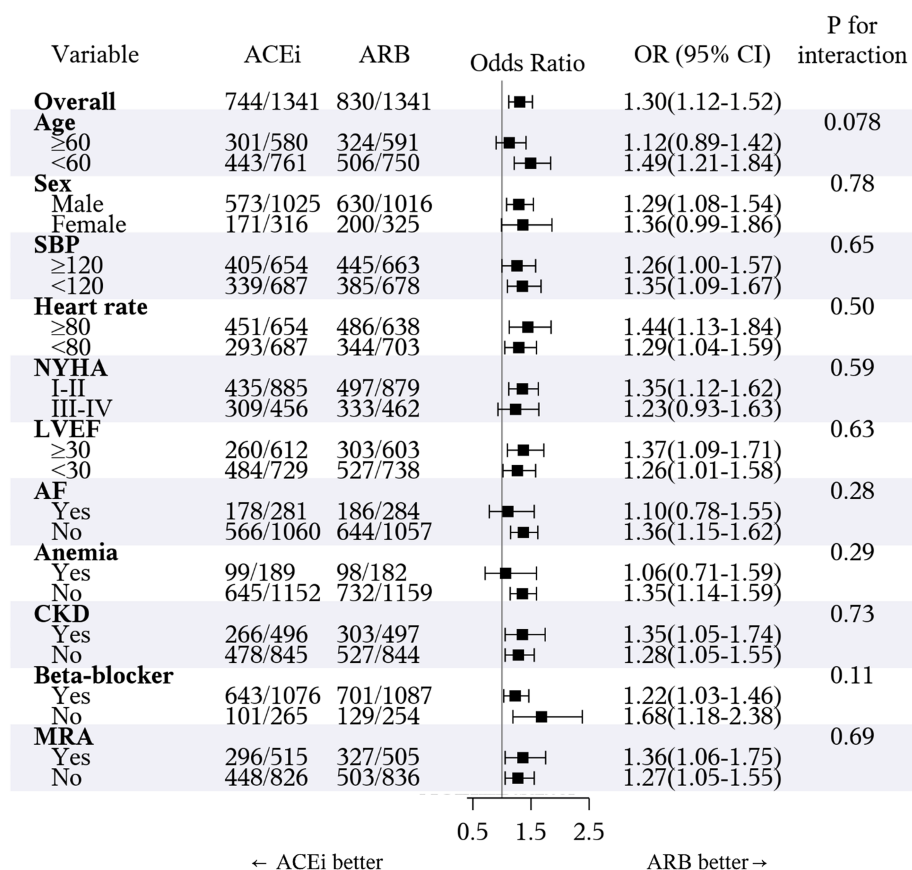


Table 2 Medications at 3 years of follow-up

| Variables | ACEi (n = 1341) | ARB (n = 1341) | P value |
|---------------------|-----------------|----------------|---------|
| Beta-blocker, n (%) | 1099 (82.0) | 1105 (82.4) | 0.76 |
| Digitalis, n (%) | 311 (25.5) | 304 (24.6) | 0.62 |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Although ACEis or ARBs have been shown to be beneficial to improve prognosis in HF patients, there is some controversy about whether ACEis or ARBs could be superior to the other. ELITE II study, VALIANT trial, OPTIMAAL study, and Swedish Heart Failure Registry did not show the superiority of ARB to ACEis in terms of survival.^{7,8,29,34} The median follow-up periods in these studies were around several years (555 days in ELITE II and 24.7 months in VALIANT). On the other hand, a propensity-matched study of the Alabama Heart Failure Project registry exhibited that ARBs had more beneficial effect on survival in HF patients than ACEis,¹² in which the follow-up period was longer than 8 years. Therefore, long-term administration of ARBs might be associated with better prognosis than that of ACEis. Importantly, whereas the aetiology of all patients in OPTIMAAL study and VALIANT study was ischaemic heart disease, only 4% of patients were ischaemic aetiology in Alabama Heart Failure Project registry. Other previous studies have suggested that non-ischaemic cardiomyopathy experienced recovery of LVEF more frequently than ischaemic cardiomyopathy.^{30,31,35} The aetiology of all of the present study population was idiopathic DCM. This aetiological homogeneity might be involved in superior effects of ARBs to ACEis.

Recently, the recovery of LVEF is often used as a surrogate endpoint in HF clinical trials.^{23,24} Patients with HF-REF had a better prognosis than those with persistent HFrEF.⁹ Several studies have indicated that ACEis or ARBs are associated with recovery of LVEF in patients with HFrEF.^{25,26} The present study demonstrated that patients treated with ARBs had not only more frequency of LVEF recovery but also greater improvement of LVEF at 3 years of follow-up than those with ACEis. These results support a previous report demonstrating superior effect of long-term use of ARBs on prognosis in HFrEF.¹¹

Haemodynamics, co-morbidities, and medication are related to recovery of cardiac function. However, in the present study, the beneficial effect of ARBs on cardiac dysfunction was independent of systolic blood pressure, heart rate, LVEF, chronic kidney disease, and concomitant use of beta-blockers and MRAs. In particular, changes in systolic blood pressure, diastolic blood pressure, and heart rate were comparable between ARB and ACEi groups (*Table 1*). Thus, it is presumed that ARBs exert the superior effect independently of haemodynamics.

In the present study, the use of ARBs was also associated with LVEF recovery regardless of biventricular pacing (Supporting Information, *Table S3*). There are possible reasons for the low rate of biventricular pacing. First, implantation of

cardiac resynchronization therapy pacing and defibrillator started in April 2004 and August 2006, respectively, in Japan.³⁶ The number of implants of these devices reached plateau in 2008. In the present study, more than half of the patients were enrolled before 2008. Second, the Japanese Cardiology Society guidelines at that time indicated that only patients with NYHA functional Class III–IV were potential candidates for these devices.

There are several differences in pharmacological action between ACEis and ARBs. Chronic therapy with ACEis leads to incomplete blockade of RAAS because of ACE-independent chymase-mediated angiotensin II production and aldosterone^{27,28} and induces activation of B₂-type bradykinin receptors.³⁷ On the other hand, ARBs inhibit RAAS by the direct blockade of angiotensin II receptor. Activation of RAAS is intimately involved in the development of cardiac dysfunction and HF. Therefore, the differences in pharmacological action might provide superiority of ARBs to ACEis in recovery of LVEF. It is important whether the superiority is related to type of drugs. In the present study, there is no significant difference in effects of candesartan, losartan, and valsartan on LVEF recovery to $\geq 40\%$ in ARB group. These data suggest that the superiority of the ARBs is class effect.

Angiotensin II receptor blockers were better tolerated than ACEis.^{7,38} Dry cough, related to increased bradykinin levels,³⁹ occurs in 5–15% of patients on ACEis but not on ARBs. Angioedema, a potentially life-threatening complication, occurs in a small percentage of patients on ACEis. In the present study, patients on ARBs continued to receive more frequently (81.3% vs. 70.6%) and changed to another class of ACEis/ARBs less frequently than those on ACEis (4.2% vs. 16.6%). We could not determine the reason of discontinuation or crossover due to the observational nature of the present study. However, a per-protocol analysis also showed superiority of ARBs to ACEis in terms of recovery from cardiac dysfunction. Thus, tolerability and side effects are not likely to affect the results of the present study. In the 2021 ESC guidelines for HF recommended that (i) an ACEi is recommended for patients with HFrEF, (ii) an ARNI is recommended as a replacement for an ACEi in patients with HFrEF, and (iii) an ARB is recommended for symptomatic patients unable to tolerate an ACEi or ARNI.⁶ The present study raises a possibility that, even in the case of ACEi tolerance, ARBs should be administered for DCM patients. To elucidate this important issue, further investigations are needed.

Study strengths and limitations

The present study has several strengths differed from previous studies. We validated the effects of ARBs and ACEis on recovery from cardiac dysfunction by not only propensity score matching analysis but also several sensitivity analyses, including multivariate Cox regression analysis, multiple

imputation analysis, and multivariate analysis, in a largest-scale registry of DCM in Japan. In addition, we evaluated reverse remodelling by using serial echocardiographic data validated by certified cardiologist.

There are several potential limitations to be acknowledged in the present study. First, we did not have information regarding mortality, cardiovascular event, and rehospitalization due to HF in the present study because the clinical personal record did not contain these data. The superior effect of ARBs to ACEis in recovered LVEF might be related to survival or other events in DCM patients. Further studies focusing on this crucial issue are needed. Second, this database does not include information regarding genetic testing. It has been reported that DCM patients harbouring titin (*TTN*)-truncating variants had better prognosis and cardiac reverse remodelling than those with lamin A/C (*LMNA*) variants.⁴⁰ There might be differences in genotypes. Third, echocardiographic assessment was not adjudicated by central monitor system because the present study used administrative database. However, the echocardiographic assessment was validated by certified cardiologists in each hospital. Fourth, the information on doses and dose response of ACEis and ARBs is important. The doses of concomitant drugs such as beta-blockers, MRAs, or loop diuretics are not negligible. In addition, the titration of beta-blockers and MRAs might help to recover LVEF. However, we could not assess them in the present study. To address these crucial points, further investigations are needed. Fifth, the present study is not a prospective randomized trial and unmeasured factors might have influenced the outcomes. The parameters in the present study were limited. However, the propensity score was adjusted for critical 23 parameters associated with prognosis of HF patients. In addition to one-to-one propensity case-matched analysis, we performed several sensitivity analyses such as complete case and multiple imputation analyses.

Despite several limitations described earlier, we analysed the largest database including more than 4000 patients with DCM in Japan and provided the first evidence of greater recovery of cardiac function by ARBs than ACEis in DCM patients.

Conclusions

The use of ARBs was associated with recovery of LVEF more frequently than ACEis among patients with DCM and reduced LVEF.

References

1. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; **316**: 1429–1435.
2. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN, SOLVD Investigators. Effect of enalapril on survival in patients with re-

Acknowledgements

This study could not have been carried out without the help, cooperation, and support of the cardiologists in the survey institutions. We thank them for allowing us to obtain the data.

Conflict of interest

H.T. reports personal fees from MSD, Astellas, Pfizer, Bristol Myers Squibb, Otsuka Pharmaceutical, Daiichi Sankyo, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Takeda Pharmaceutical, Bayer Yakuhin, Novartis Pharma, Kowa Pharmaceuticals, Teijin Pharma, Medical Review Co., and Japanese Journal of Clinical Medicine; non-financial support from Actelion Pharmaceuticals, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Daiichi Sankyo, IQVIA Services Japan, and Omron Healthcare Co.; and grants from Astellas, Novartis Pharma, Daiichi Sankyo, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Teijin Pharma, and MSD, outside the submitted work. The other authors declare no conflicts of interest associated with this manuscript.

Funding

This work was supported by grants from Health Sciences Research Grants from the Japanese Ministry of Health, Labour and Welfare [Comprehensive Research on Cardiovascular Diseases (20FC1051)] and the Japan Agency for Medical Research and Development (AMED) grant (19ek0109367h0002 and 20ek0109367h0003) to H.T.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Medication among ACEi/ARB group.

Table S2. Primary and secondary outcomes in imputed datasets.

Table S3. LVEF recovery in patients without biventricular pacing.

Figure S1. Supporting information.

- duced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; **325**: 293–302.
3. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K, CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; **362**: 772–776.
 4. Maggioni AP, Anand I, Gottlieb SO, Latini R, Tognoni G, Cohn JN, Val-HeFT Investigators (Valsartan Heart Failure Trial). Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol* 2002; **40**: 1414–1421.
 5. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**: 993–1004.
 6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibellund A, ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; **42**: 3599–3726.
 7. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klingler GH, Neaton J, Sharma D, Thiyagarajan B. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; **355**: 1582–1587.
 8. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM, Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; **349**: 1893–1906.
 9. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**: e147–e239.
 10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members, Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**: 891–975.
 11. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snively DB, Chang PI. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997; **349**: 747–752.
 12. Zhang Y, Fonarow GC, Sanders PW, Farahmand F, Allman RM, Aban IB, Love TE, Levesque R, Kilgore ML, Ahmed A. A propensity-matched study of the comparative effectiveness of angiotensin receptor blockers versus angiotensin-converting enzyme inhibitors in heart failure patients age ≥ 65 years. *Am J Cardiol* 2011; **108**: 1443–1448.
 13. McKenna WJ, Maron BJ, Thiene G. Classification, epidemiology, and global burden of cardiomyopathies. *Circ Res* 2017; **121**: 722–730.
 14. Matsumura Y, Takata J, Kitaoka H, Kubo T, Baba Y, Hoshikawa E, Hamada T, Okawa M, Hitomi N, Sato K, Yamasaki N, Yabe T, Furuno T, Nishinaga M, Doi Y. Long-term prognosis of dilated cardiomyopathy revisited: an improvement in survival over the past 20 years. *Circ J* 2006; **70**: 376–383.
 15. Luk A, Ahn E, Soor GS, Butany J. Dilated cardiomyopathy: a review. *J Clin Pathol* 2009; **62**: 219–225.
 16. Hellawell JL, Margulies KB. Myocardial reverse remodeling. *Cardiovasc Ther* 2012; **30**: 172–181.
 17. Punnoose LR, Givertz MM, Lewis EF, Pratibhu P, Stevenson LW, Desai AS. Heart failure with recovered ejection fraction: a distinct clinical entity. *J Card Fail* 2011; **17**: 527–532.
 18. Florea VG, Rector TS, Anand IS, Cohn JN. Heart failure with improved ejection fraction: clinical characteristics, correlates of recovery, and survival: results from the Valsartan Heart Failure Trial. *Circ Heart Fail* 2016; **9**.
 19. Kalogeropoulos AP, Fonarow GC, Georgiopoulos V, Burkman G, Siwamogsatham S, Patel A, Li S, Papadimitriou L, Butler J. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. *JAMA Cardiol* 2016; **1**: 510–518.
 20. Jorgensen ME, Andersson C, Vasan RS, Kober L, Abdulla J. Characteristics and prognosis of heart failure with improved compared with persistently reduced ejection fraction: a systematic review and meta-analyses. *Eur J Prev Cardiol* 2018; **25**: 366–376.
 21. Park CS, Park JJ, Mebazaa A, Oh IY, Park HA, Cho HJ, Lee HY, Kim KH, Yoo BS, Kang SM, Baek SH, Jeon ES, Kim JJ, Cho MC, Chae SC, Oh BH, Choi DJ. Characteristics, outcomes, and treatment of heart failure with improved ejection fraction. *J Am Heart Assoc* 2019; **8**: e011077.
 22. Basuray A, French B, Ky B, Vorovich E, Olt C, Sweitzer NK, Cappola TP, Fang JC. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. *Circulation* 2014; **129**: 2380–2387.
 23. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. *J Am Coll Cardiol* 2010; **56**: 392–406.
 24. Konstam MA. Reliability of ventricular remodeling as a surrogate for use in conjunction with clinical outcomes in heart failure. *Am J Cardiol* 2005; **96**: 867–871.
 25. Wong M, Staszewsky L, Latini R, Barlera S, Volpi A, Chiang YT, Benza RL, Gottlieb SO, Kleemann TD, Rosconi F, Vandervoort PM, Cohn JN, Val-HeFT Heart Failure Trial Investigators. Valsartan benefits left ventricular structure and function in heart failure: Val-HeFT echocardiographic study. *J Am Coll Cardiol* 2002; **40**: 970–975.
 26. Enzan N, Matsushima S, Ide T, Kaku H, Tohyama T, Funakoshi K, Higo T, Tsutsui H. The use of angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers is associated with the recovered ejection fraction in patients with dilated cardiomyopathy. *Int Heart J* 2021; **64**: 801–810.
 27. Cicoira M, Zanolla L, Franceschini L, Rossi A, Golia G, Zeni P, Caruso B, Zardini P. Relation of aldosterone “escape” despite angiotensin-converting enzyme inhibitor administration to impaired exercise capacity in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 2002; **89**: 403–407.
 28. Dzau VJ, Bernstein K, Celermajer D, Cohen J, Dahlof B, Deanfield J, Diez J, Drexler H, Ferrari R, van Gilst W,

- Hansson L, Hornig B, Husain A, Johnston C, Lazar H, Lonn E, Luscher T, Mancini J, Mimran A, Pepine C, Rabelink T, Remme W, Ruilope L, Ruzicka M, Schunkert H, Swedberg K, Unger T, Vaughan D, Weber M, Working Group on Tissue Angiotensin-converting enzyme, International Society of Cardiovascular Pharmacotherapy. The relevance of tissue angiotensin-converting enzyme: manifestations in mechanistic and endpoint data. *Am J Cardiol* 2001; **88**: 11L–20L.
29. Dickstein K, Kjekshus J, OPTIMAAL Steering Committee, for the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet* 2002; **360**: 752–760.
30. Merlo M, Pyxaras SA, Pinamonti B, Barbati G, Di Lenarda A, Sinagra G. Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment. *J Am Coll Cardiol* 2011; **57**: 1468–1476.
31. Lupon J, Diez-Lopez C, de Antonio M, Domingo M, Zamora E, Moliner P, Gonzalez B, Santesmases J, Troya MI, Bayes-Genis A. Recovered heart failure with reduced ejection fraction and outcomes: a prospective study. *Eur J Heart Fail* 2017; **19**: 1615–1623.
32. Enzan N, Matsushima S, Ide T, Kaku H, Tohyama T, Funakoshi K, Higo T, Tsutsui H. Clinical characteristics and contemporary management of patients with cardiomyopathies in Japan—report from a national registry of clinical personal records. *Circ Rep* 2021; **3**: 142–152.
33. Leyrat C, Seaman SR, White IR, Douglas I, Smeeth L, Kim J, Resche-Rigon M, Carpenter JR, Williamson EJ. Propensity score analysis with partially observed covariates: how should multiple imputation be used? *Stat Methods Med Res* 2019; **28**: 3–19.
34. Savarese G, Edner M, Dahlstrom U, Perrone-Filardi P, Hage C, Cosentino F, Lund LH. Comparative associations between angiotensin converting enzyme inhibitors, angiotensin receptor blockers and their combination, and outcomes in patients with heart failure and reduced ejection fraction. *Int J Cardiol* 2015; **199**: 415–423.
35. Wilcox JE, Fonarow GC, Yancy CW, Albert NM, Curtis AB, Heywood JT, Inge PJ, McBride ML, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Gheorghiade M. Factors associated with improvement in ejection fraction in clinical practice among patients with heart failure: findings from IMPROVE HF. *Am Heart J* 2012; **163**: 49–56 e2.
36. Yokoshiki H, Shimizu A, Mitsuhashi T, Furushima H, Sekiguchi Y, Manaka T, Nishii N, Ueyama T, Morita N, Nitta T, Okumura K, Members of the Implantable Cardioverter-Defibrillator (ICD) Committee of the Japanese Heart Rhythm Society. Trends and determinant factors in the use of cardiac resynchronization therapy devices in Japan: analysis of the Japan cardiac device treatment registry database. *J Arrhythm* 2016; **32**: 486–490.
37. Morris SD, Yellon DM. Angiotensin-converting enzyme inhibitors potentiate preconditioning through bradykinin B₂ receptor activation in human heart. *J Am Coll Cardiol* 1997; **29**: 1599–1606.
38. Goldberg AI, Dunlay MC, Sweet CS. Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydrochlorothiazide, atenolol, felodipine ER, and angiotensin-converting enzyme inhibitors for the treatment of systemic hypertension. *Am J Cardiol* 1995; **75**: 793–795.
39. Givertz MM. Manipulation of the renin-angiotensin system. *Circulation* 2001; **104**: E14–E18.
40. Tobita T, Nomura S, Fujita T, Morita H, Asano Y, Onoue K, Ito M, Imai Y, Suzuki A, Ko T, Satoh M, Fujita K, Naito AT, Furutani Y, Toko H, Harada M, Amiya E, Hatano M, Takimoto E, Shiga T, Nakanishi T, Sakata Y, Ono M, Saito Y, Takashima S, Hagiwara N, Aburatani H, Komuro I. Genetic basis of cardiomyopathy and the genotypes involved in prognosis and left ventricular reverse remodeling. *Sci Rep* 2018; **8**: 1998.