The primary outcome occurred in 51 patients (27.3%) of the control group and 12 patients (20.7%) of the standard-dose group. HR for the primary outcome in the standard-dose group was 0.610 (95% CI 0.320–1.160; log-rank test $p = 0.13$) (Fig. 1A). Another composite major outcome occurred in 75 patients (40.1%) of the control group and 15 patients (25.9%) of the standard-dose group. HR for this composite major outcome in the standard-dose group was 0.529 (95% CI 0.303–0.924; log-rank test $p = 0.018$) (Fig. 1B).

Association between baseline characteristics and clinical outcomes

Table 2 shows HR of each clinical factor for the primary outcome and another major composite outcome in a univariate analysis. Aging, diabetes mellitus, increases in creatinine, BNP, LV mass index, and LA dimension, and decreases in BMI, hemoglobin, and eGFR were risk factors for both clinical outcomes. In addition, cerebrovascular disease and an increase in LV end-diastolic dimension were associated with the primary outcome, and a decrease in EF was associated with another major composite outcome.

In a multivariable analysis (Table 3), BMI, diabetes mellitus, and LA dimension were independently associated with both clinical outcomes. In addition, LV mass index was an independent risk factor for the primary endpoint, and BNP and prescription of standard-dose carvedilol were for another major composite outcome.

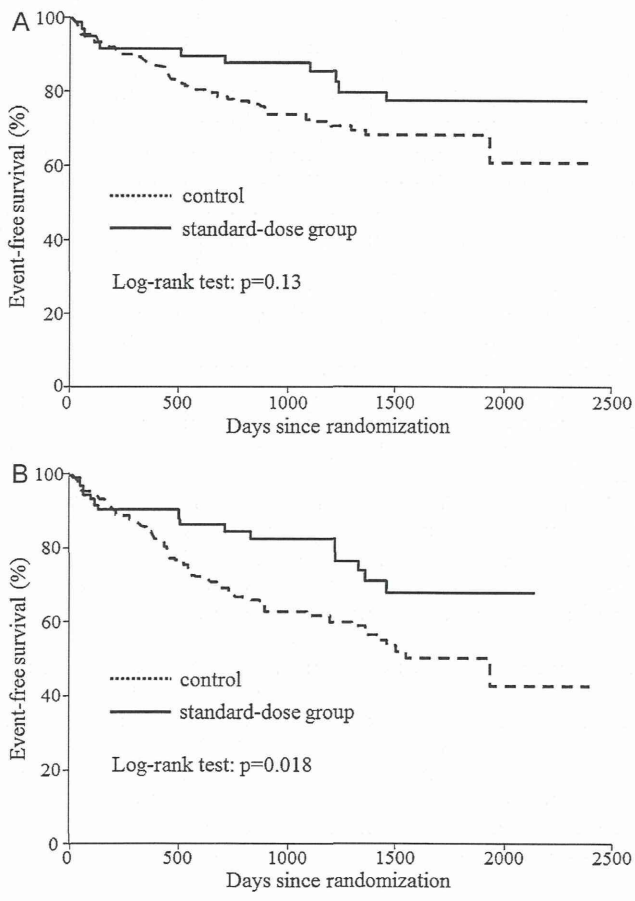


Fig. 1. Kaplan–Meier curves of the primary outcome (a composite of cardiovascular death and unplanned hospitalization for heart failure) (A) and another major composite outcome (a composite of cardiovascular death and unplanned hospitalization for any cardiovascular causes) (B). The curves of standard-dose group in both figures were reproduced from Yamamoto et al. [3].

Table 2
Results of univariate Cox proportional hazards models for the clinical outcomes.

	HR	(95% CI)	*p*-Value
Primary endpoint			
Age	1.031	(1.004–1.059)	0.027
Female	1.056	(0.638–1.750)	0.83
NYHA	1.212	(0.759–1.934)	0.42
SAS score	0.912	(0.788–1.055)	0.21
Heart rate	1.007	(0.987–1.026)	0.51
Changes in heart rate a year after the enrollment	1.009	(0.991–1.029)	0.32
Systolic blood pressure	0.998	(0.986–1.010)	0.73
Changes in systolic blood pressure a year after the enrollment	1.005	(0.993–1.018)	0.43
Diastolic blood pressure	0.984	(0.964–1.005)	0.13
Body mass index	0.928	(0.878–0.982)	0.0090
Etiology of heart failure			
Ischemic	1.361	(0.724–2.556)	0.34
Morbidity			
Hypertension	0.695	(0.389–1.244)	0.22
Ischemic heart disease	1.164	(0.672–2.015)	0.59
Atrial fibrillation	1.378	(0.836–2.274)	0.21
Diabetes mellitus	2.262	(1.377–3.716)	0.0013
Dyslipidemia	0.937	(0.567–1.549)	0.80
Cerebrovascular disease	2.050	(1.090–3.855)	0.026
History of hospitalization for heart failure	1.683	(0.981–2.887)	0.059
Medications			
Standard-dose carvedilol	0.615	(0.326–1.161)	0.13
ACEI	0.863	(0.468–1.592)	0.64
ARB	1.018	(0.616–1.681)	0.95
ACEI or ARB	1.010	(0.587–1.739)	0.97
Diuretics	1.325	(0.783–2.243)	0.29
Mineralocorticoid receptor blockers	1.341	(0.776–2.317)	0.29
Digoxin	0.825	(0.439–1.549)	0.55
Ca channel blocker	1.271	(0.774–2.088)	0.34
Hemoglobin	0.759	(0.663–0.868)	<0.0001
Serum creatinine level	3.161	(2.011–4.968)	<0.0001
Estimated glomerular filtration rate	0.976	(0.962–0.989)	0.0004
B-type natriuretic peptide	1.001	(1.001–1.002)	<0.0001
Norepinephrine	1.000	(1.000–1.001)	0.098
Left ventricular end-diastolic dimension	1.040	(1.007–1.074)	0.017
Left ventricular ejection fraction	0.981	(0.958–1.005)	0.12
Left ventricular mass index	1.014	(1.006–1.022)	0.0007
Relative wall thickness	2.327	(0.247–21.903)	0.46
Left atrial dimension	1.048	(1.019–1.077)	0.0009
Composite of cardiovascular death and unplanned hospitalization for any cardiovascular causes			
Age	1.023	(1.002–1.045)	0.035
Female	1.020	(0.671–1.549)	0.93
NYHA	1.192	(0.807–1.760)	0.38
SAS score	0.949	(0.844–1.067)	0.38
Heart rate	1.004	(0.987–1.020)	0.66
Changes in heart rate a year after the enrollment	1.014	(0.999–1.030)	0.072
Systolic blood pressure	1.005	(0.994–1.015)	0.38
Changes in systolic blood pressure a year after the enrollment	1.006	(0.996–1.017)	0.23
Diastolic blood pressure	1.001	(0.984–1.017)	0.93
Body mass index	0.952	(0.909–0.998)	0.040
Etiology of heart failure			
Ischemic	1.306	(0.770–2.215)	0.32
Morbidity			
Hypertension	0.785	(0.478–1.291)	0.34
Ischemic heart disease	1.287	(0.823–2.012)	0.27
Atrial fibrillation	1.292	(0.854–1.954)	0.22
Diabetes mellitus	1.919	(1.260–2.923)	0.0024
Dyslipidemia	1.422	(0.940–2.150)	0.096
Cerebrovascular disease	1.721	(0.987–2.999)	0.056
History of hospitalization for heart failure	1.276	(0.829–1.966)	0.27

Table 2 (*Continued*)

	HR	(95% CI)	*p*-Value
Medications			
Standard-dose carvedilol	0.518	(0.297–0.903)	0.021
ACEI	0.980	(0.601–1.597)	0.93
ARB	1.107	(0.729–1.679)	0.63
ACEI or ARB	1.215	(0.764–1.931)	0.41
Diuretics	0.972	(0.637–1.482)	0.89
Mineralocorticoid receptor blockers	0.975	(0.598–1.591)	0.92
Digoxin	0.973	(0.586–1.615)	0.92
Ca channel blocker	1.043	(0.690–1.577)	0.84
Hemoglobin	0.853	(0.764–0.952)	0.0047
Serum creatinine level	2.624	(1.757–3.918)	<0.0001
Estimated glomerular filtration rate	0.977	(0.966–0.988)	<0.0001
B-type natriuretic peptide	1.001	(1.001–1.002)	<0.0001
Norepinephrine	1.000	(1.000–1.001)	0.23
Left ventricular end-diastolic dimension	1.019	(0.991–1.048)	0.19
Left ventricular ejection fraction	0.976	(0.957–0.996)	0.022
Left ventricular mass index	1.011	(1.004–1.018)	0.0033
Relative wall thickness	2.865	(0.443–18.514)	0.27
Left atrial dimension	1.031	(1.005–1.057)	0.019

For continuous predictors, HR per unit is shown. HR, hazard ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NYHA, New York Heart Association; SAS, specific activity scale.

Interaction between the risk factors and the effects of standard-dose carvedilol

Figs. 2 and 3 show the interaction between the factors associated with both clinical outcomes in a univariate analysis and the effects of standard-dose carvedilol. If the factors are continuous variables, the subjects were divided by the median value.

Fig. 2 shows the interaction regarding the primary outcome, and there was no interaction with any clinical factors except LA dimension. The administration of standard-dose carvedilol was associated with unadjusted HR 0.263 (95% CI: 0.080 to 0.859) (Fig. 2A) and covariate adjusted 0.264 (0.080 to 0.876) (Fig. 2B) for the primary outcome in the patients with LA diameter ≥ the median value (43.2 mm). In contrast, unadjusted and adjusted HRs were 1.123 (0.501 to 2.514) and 1.067 (0.472 to 2.412) in those with LA diameter < 43.2 mm. A *p*-value for interaction was 0.046 (unadjusted) and 0.058 (adjusted).

For another major composite outcome (Fig. 3), the effects of standard-dose carvedilol also tended to be different between the patients with LA diameter ≥ and <43.2 mm [$p = 0.076$ (unadjusted, Fig. 3A) and $p = 0.12$ (adjusted, Fig. 3B)]. Unadjusted and adjusted HRs were 0.257 (0.092 to 0.715) and 0.277 (0.099 to 0.777) in those with LA diameter ≥ 43.2 mm, and 0.783 (0.393 to 1.561) and 0.747 (0.372 to 1.500) in those with LA diameter < 43.2 mm.

The neutral effects of standard-dose carvedilol were observed across the other factors.

Table 3
Results of multivariable Cox proportional hazards models for the clinical outcomes.

	HR	(95% CI)	*p*-Value
Primary endpoint			
Age	1.110	(0.828–1.487)	0.49
Body mass index	0.865	(0.791–0.945)	0.0013
Diabetes mellitus	3.021	(1.730–5.263)	<0.0001
Standard-dose carvedilol	0.874	(0.448–1.704)	0.69
Hemoglobin	0.913	(0.788–1.057)	0.22
Estimated glomerular filtration rate	0.992	(0.979–1.006)	0.27
B-type natriuretic peptide	1.000	(1.000–1.001)	0.29
Left ventricular mass index	1.013	(1.004–1.023)	0.0052
Left atrial dimension	1.052	(1.021–1.085)	0.0010
Composite of cardiovascular death and unplanned hospitalization for any cardiovascular causes			
Age	1.110	(0.879–1.401)	0.38
Body mass index	0.926	(0.865–0.992)	0.028
Diabetes mellitus	2.237	(1.420–3.521)	0.0005
Standard-dose carvedilol	0.542	(0.301–0.975)	0.041
Hemoglobin	1.028	(0911–1.160)	0.65
Estimated glomerular filtration rate	0.989	(0.977–1.001)	0.062
B-type natriuretic peptide	1.001	(1.000–1.002)	0.0024
Left ventricular mass index	1.007	(0.999–1.016)	0.092
Left atrial dimension	1.028	(1.000–1.057)	0.049

For continuous predictors, HR per unit is shown. HR, hazard ratio; CI, confidence interval.

Discussion

Predictors of clinical outcomes in patients with HFPEF

Aging, decreased BMI, diabetes mellitus, anemia, renal dysfunction, elevated plasma BNP, LV hypertrophy, and LA dilatation were risk factors for both the primary outcome and another major composite outcome in a univariate analysis. A multivariable analysis revealed that decreased BMI, diabetes mellitus, and LA dilatation were independent risk factors for both clinical outcomes. All of the factors raised in the univariate analysis have been reported as the risk factors for morbidity and mortality of patients with HFPEF in studies in Western countries [5–9], and our results confirmed that the same factors are the risks for Japanese patients with HFPEF, which is partly compatible with a previous study in Japan [10]. Present results also indicate that the patients' characteristics in this study are not far from those of other studies.

Obesity is a risk for incident of heart failure; however, the prognosis of heart failure is better in patients with high BMI than low BMI, and this is termed as obesity paradox [11]. An increase in BMI was associated with the incidence of HFPEF in hypertensive or diabetic Japanese patients [12,13], and the current result has confirmed that obesity paradox is also observed in Japanese HFPEF patients. However, this does not simply indicate that a gain of body weight improves the prognosis of HFPEF. Neither BMI nor triceps skinfold thickness independently predicts long-term survival of elderly patients with heart failure, whereas a larger midarm muscle area does [14]. A recent study demonstrated that geriatric nutritional risk index is more closely associated with mortality of Japanese HFPEF patients than BMI [15]. Thus, nutritional status rather than body weight is likely to have a clinical impact on prognosis.

The improvement in prognosis of the patients with HFREF by β-blockers is well acknowledged, and the beneficial effects of β-blockers are associated with the reduction in heart rate [16]. The Systolic Heart failure treatment with the *If* inhibitor ivabradine Trial (SHIFT) reported that the heart rate reduction by a specific inhibitor of the *If* current in the sinoatrial node improved the prognosis of HFREF patients [17]. In contrast, the ivabradine-induced reduction of heart rate did not improve the clinical outcome of patients with coronary artery disease and reduced EF [18], and a subgroup analysis of Cardiac Insufficiency Bisoprolol Study II (CIBIS II) showed that the beneficial effects of β-blocker in HFREF cannot be attributed only to the reduction in heart rate [19]. Therefore, the cause-and-effect relationship between changes in heart rate and clinical outcomes of HFREF remains unclear. In J-DHF study, the changes in heart rate at one year after the randomization were not associated with the clinical outcomes of HFPEF patients (Table 2), and were not significantly different between the control and standard-dose groups (data not shown). Therefore, the beneficial effects of standard-dose carvedilol in HFPEF are unlikely provided through the reduction of heart rate.

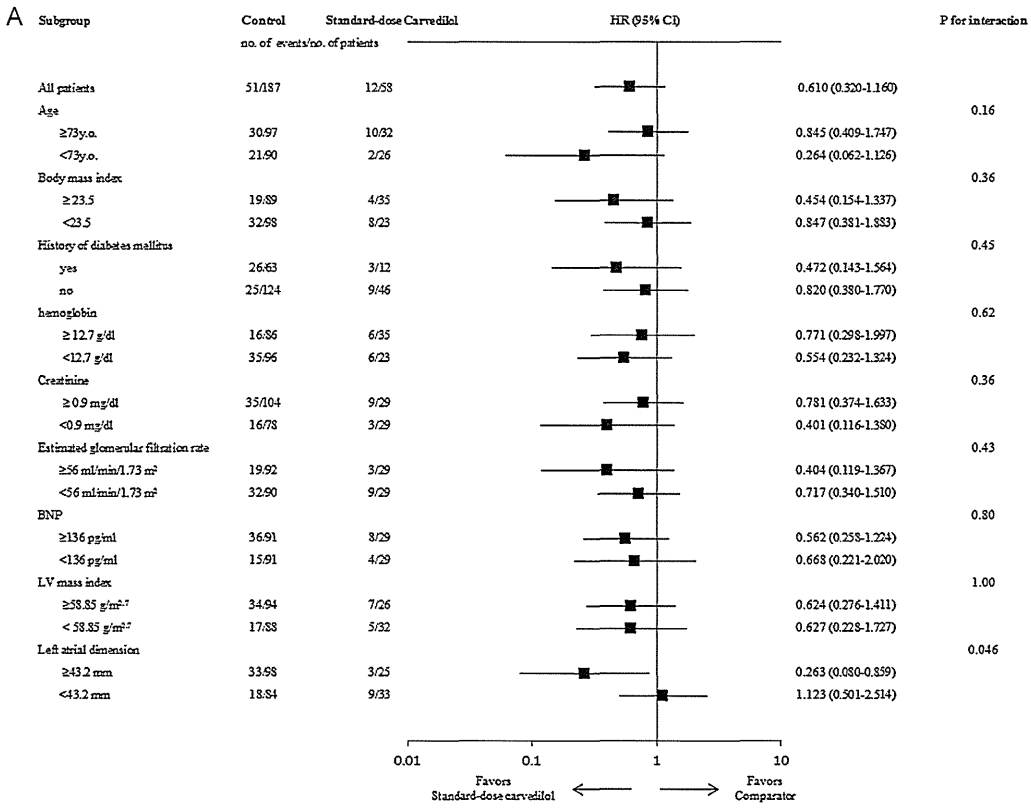
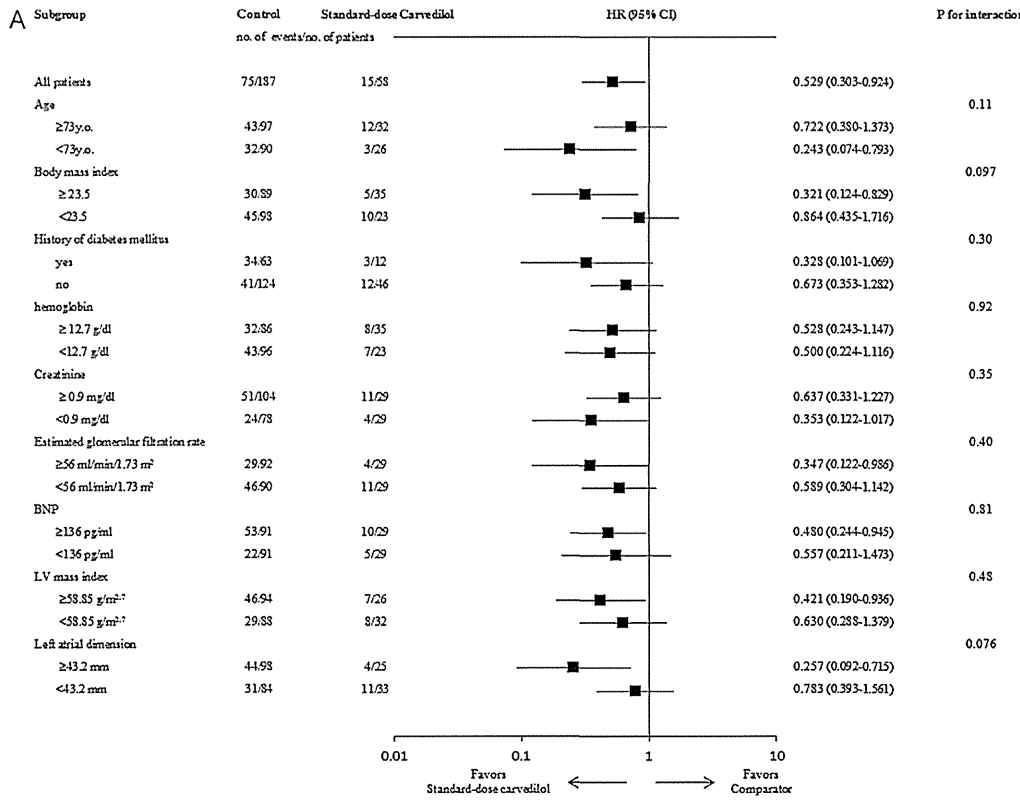


Fig. 2. (A) Unadjusted analysis of the primary outcome in subgroups. (B) Adjusted analysis for prespecified covariates (age, sex, etiology, and left ventricular ejection fraction). The plot shows hazard ratios and 95% confidence intervals. Statistical significance for interaction implies that the factor is predictive of effective beta-blockers. Data are missing for some patients in some subgroups. CI, confidence interval; HR, hazard ratio; BNP, B-type natriuretic peptide; LV, left ventricular.



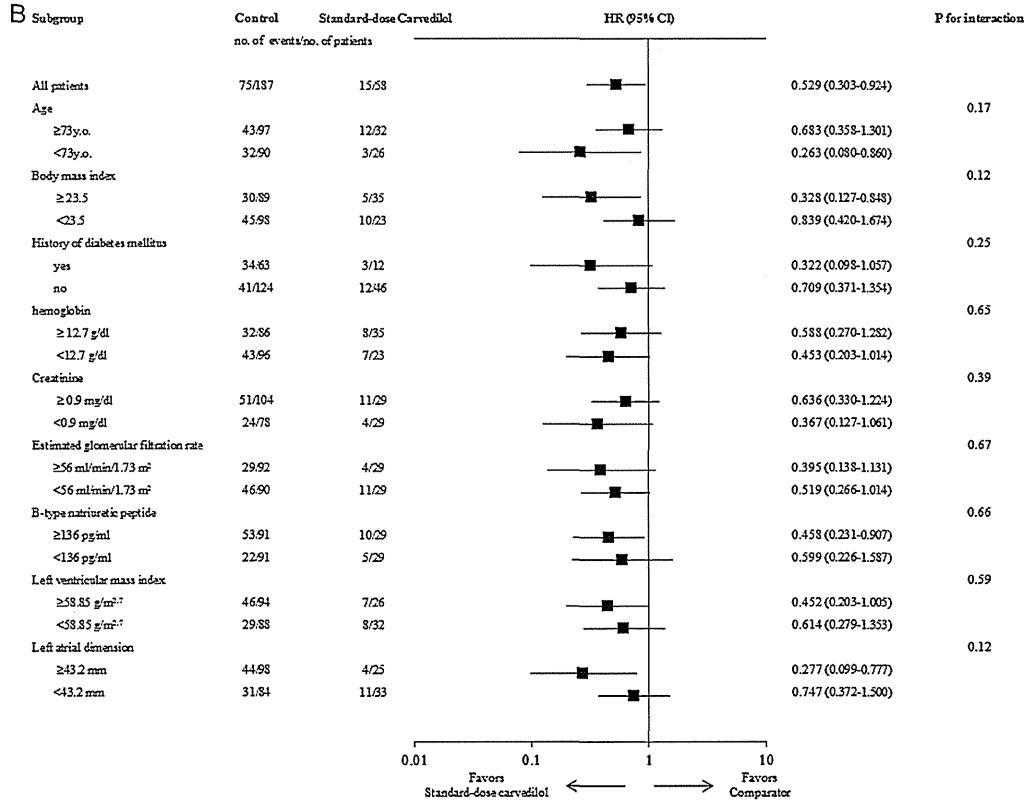


Fig. 3. (A) Unadjusted analysis of another major composite outcome in subgroups. (B) Adjusted analysis for prespecified covariates (age, sex, etiology, and left ventricular ejection fraction). The plot shows hazard ratios and 95% confidence intervals. Statistical significance for interaction implies that the factor is predictive of effective beta-blockers. Data are missing for some patients in some subgroups. CI, confidence interval; HR, hazard ratio; BNP, B-type natriuretic peptide; LV, left ventricular.

Interaction between the risk factors and the effects of standard-dose carvedilol

The elevation of plasma BNP level, LV hypertrophy, and LA dilatation were associated with clinical outcomes in this study. In particular, LA dilatation was an independent risk factor for both clinical outcomes. LA dilatation is attributed to advanced LV diastolic dysfunction and elevated LA pressure [20,21], and LV hypertrophy and elevated BNP level also indicate LV diastolic dysfunction in subjects with preserved EF [22,23]. It is plausible that advanced LV diastolic dysfunction is related to prognosis of HFPEF. The current result suggested that LA dilatation interacted with the effects of standard-dose carvedilol. The risk reduction in patients with large LA was great as compared to those with small LA. Although there was no interaction with LV mass index or BNP level, this result suggests that the beneficial effects of standard-dose carvedilol are provided in HFPEF patients with advanced rather than mild diastolic dysfunction.

Elderly HFREF patients are at high risk of morbidity and mortality; however, they are often excluded from the subjects in randomized studies to assess the effects of pharmacological intervention on HFREF, and thus, the therapeutic effects on elderly patients are not extensively studied. This may result in less prescription of β-blockers in elderly patients with heart failure [24]. In this study, the exclusion criteria did not include age, and consequently the median value was 73 years; the most advanced age was 93 years in the control group and 89 years in the standard-dose group. The current study demonstrated that aging was also one of the risk factors for clinical outcomes of HFPEF patients (Table 2), and the lack of the interaction with age (Figs. 2 and 3) suggests that the beneficial effects of standard-dose carvedilol are expected even in elderly patients with HFPEF.

Diabetes mellitus was one of the independent risk factors in this study. Previous studies have reported that β-blockers increased the risk of subsequent onset of diabetes mellitus [25,26], and β-blockers are often avoided in patients with diabetes mellitus. However, a randomized trial showed that carvedilol improved glucose and lipid metabolism [27]. This study showed a lack of the interaction of diabetes mellitus with the effects of standard-dose carvedilol in HFPEF patients, although patients with uncontrolled diabetes mellitus were excluded from the study. Thus, even in HFPEF patients with diabetes mellitus, standard-dose carvedilol is expected to provide beneficial effects if diabetes mellitus is appropriately controlled.

Renal dysfunction and anemia were also raised as risk factors in this study, and anemia may be partly attributed to renal dysfunction. Previous studies have shown beneficial effects of β-blockers in HFREF patients with chronic kidney disease [28]. Although patients with severe renal dysfunction were excluded in this study, there was no interaction between eGFR and the effects of standard-dose carvedilol. β-Blockers may be efficacious in HFPEF as well as HFREF even if patients have chronic kidney disease.

Study limitations

This secondary analysis study has several limitations. First, the J-DHF study is not a community-based study. Cohort studies and randomized clinical trials have shown different pathophysiology of HFPEF. For example, mode of death is different among studies [29,30]. The risk factors of HFPEF raised in this study may not be generalizable to the entire Japanese or world-wide population. Second, the number of the study subjects was small. Third, the control group of this secondary analysis study consists of HFPEF patients without carvedilol and with the administration of low-dose carvedilol. Although the combined grouping was not designed before the subgroup analysis, the demographic profile and the occurrence of clinical events were compatible between HFPEF patients without carvedilol and with the administration of low-dose carvedilol. In addition, baseline patient characteristics of the control and standard-dose groups in this study were not different as shown in Table 1, and thus, such combined grouping may not affect the conclusion of this study.

Conclusion

Aging, decreased BMI, diabetes mellitus, anemia, renal dysfunction, increased plasma BNP, LV hypertrophy, and LA dilatation are associated with clinical outcomes of HFPEF, and decreased BMI, diabetes mellitus, and LA dilatation were independent risk factors. The risk reduction by standard-dose carvedilol was great in patients with large LA as compared to those with small LA. The current results suggest that advanced LV diastolic dysfunction as indicated by LA dilatation exacerbates prognosis of HFPEF, and that the standard-dose carvedilol exerts greater reduction of the incidence of clinical outcomes in HFPEF patients with advanced rather than mild diastolic dysfunction.

Conflict of interest

Dr Yamamoto reported receiving grant support and lecturer's fees from Daiichi Sankyo, Otsuka, Pfizer, Mitsubishi Tanabe, Novartis, Takeda, Boston, and St. Jude Medical for the past year. Dr Sakata reported receiving lecturer's fees from Daiichi Sankyo, Otsuka, and Takeda for the past year. Dr Hori reported receiving grant support and lecturer's fees from Daiichi Sankyo, Bayer, Boehringer Ingelheim, Ono, West Japan Oncology Group, Osaka Medical Association, Riken, and Japan Foundation for the Promotion of International Medical Research Cooperation for the past year. Drs Origasa, Suzuki, Takahashi, Shinozaki, Watanabe, Izumi, and Taira reported no conflict of interest.

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Appendix A.

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