



## Influence of Left Ventricular Ejection Fraction on the Effects of Supplemental Use of Angiotensin Receptor Blocker Olmesartan in Hypertensive Patients With Heart Failure

Masanobu Miura, MD, PhD; Yasuhiko Sakata, MD, PhD; Satoshi Miyata, PhD;  
Nobuyuki Shiba, MD, PhD; Jun Takahashi, MD, PhD; Kotaro Nochioka, MD, PhD;  
Tsuyoshi Takada, MD, PhD; Chiharu Saga; Tsuyoshi Shinozaki, MD, PhD;  
Masafumi Sugi, MD, PhD; Makoto Nakagawa, MD, PhD; Nobuyo Sekiguchi, MD, PhD;  
Tatsuya Komaru, MD, PhD; Atsushi Kato, MD, PhD; Mitsumasa Fukuchi, MD, PhD;  
Eiji Nozaki, MD, PhD; Tetsuya Hiramoto, MD, PhD; Kanichi Inoue, MD, PhD;  
Toshikazu Goto, MD, PhD; Masatoshi Ohe, MD, PhD; Kenji Tamaki, MD, PhD;  
Setsuro Ibayashi, MD, PhD; Nobumasa Ishide, MD, PhD; Yukio Maruyama, MD, PhD;  
Ichiro Tsuji, MD, PhD; Hiroaki Shimokawa, MD, PhD on behalf of the SUPPORT Trial Investigators

**Background:** There is no robust evidence of pharmacological interventions to improve mortality in heart failure (HF) patients with preserved left ventricular ejection fraction (LVEF) (HFpEF). In this subanalysis study of the SUPPORT Trial, we addressed the influence of LVEF on the effects of olmesartan in HF.

**Methods and Results:** Among 1,147 patients enrolled in the SUPPORT Trial, we examined 429 patients with reduced LVEF (HFrEF, LVEF <50%) and 709 with HFpEF (LVEF ≥50%). During a median follow-up of 4.4 years, 21.9% and 12.5% patients died in the HFrEF and HFpEF groups, respectively. In HFrEF patients, the addition of olmesartan to the combination of angiotensin-converting enzyme inhibitor (ACEI) and  $\beta$ -blocker (BB) was associated with increased incidence of death (hazard ratio (HR) 2.26,  $P=0.002$ ) and worsening renal function (HR 2.01,  $P=0.01$ ), whereas its addition to ACEI or BB alone was not. In contrast, in HFpEF patients, the addition of olmesartan to BB alone was significantly associated with reduced mortality (HR 0.32,  $P=0.03$ ), whereas with ACEIs alone or in combination with BB and ACEI was not. The linear mixed-effect model showed that in HFpEF, the urinary albumin/creatinine ratio was unaltered when BB were combined with olmesartan, but significantly increased when not combined with olmesartan ( $P=0.01$ ).

**Conclusions:** LVEF substantially influences the effects of additive use of olmesartan, with beneficial effects noted when combined with BB in hypertensive HFpEF patients. (*Circ J* 2016; **80**: 2155–2164)

**Key Words:** Angiotensin II receptor blocker; Heart failure with preserved ejection fraction; Hypertension; Olmesartan; Prognosis

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Department of Cardiovascular Medicine (M.M., Y.S., J.T., K.N., H.S.), Department of Evidence-based Cardiovascular Medicine (S.M., C.S.), Tohoku University Graduate School of Medicine, Sendai; Department of Cardiovascular Medicine, International University of Health and Welfare Hospital, Nasushiobara (N. Shiba, T.T.); Cardiovascular Division, Sendai Medical Center, National Hospital Organization, Sendai (T.S.); Cardiovascular Division, Iwaki Kyouritsu Hospital, Iwaki (M.S.); Department of Cardiology, Iwate Prefectural Isawa Hospital, Oshu (M.N.); Cardiovascular Division, Joetsu Community Medical Center, Joetsu (N. Sekiguchi); Department of Cardiology, Miyagi Cardiovascular and Respiratory Center, Kurihara (T.K.); Cardiovascular Division, Sendai Open Hospital, Sendai (A.K.); Cardiovascular Division, JR Sendai Hospital, Sendai (M.F.); Department of Cardiology, Iwate Prefectural Central Hospital, Morioka (E.N.); Cardiovascular Division, Osaki Citizen Hospital, Osaki (T.H.); Cardiovascular Division, South Miyagi Medical Center, Ogawara (K.I.); Department of Cardiology, Yamagata Prefectural Central Hospital, Yamagata (T.G.); Cardiovascular Division, Kojirakawa Shieido Hospital, Yamagata (M.O.); Cardiology Department, Iwate Health Service Association, Morioka (K.T.); Seiai Rehabilitation Hospital, Onojo (S.I.); Sendai Shirayuri Women's College, Sendai (N.I.); Hoshi General Hospital, Koriyama (Y.M.); and Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai (I.T.), Japan

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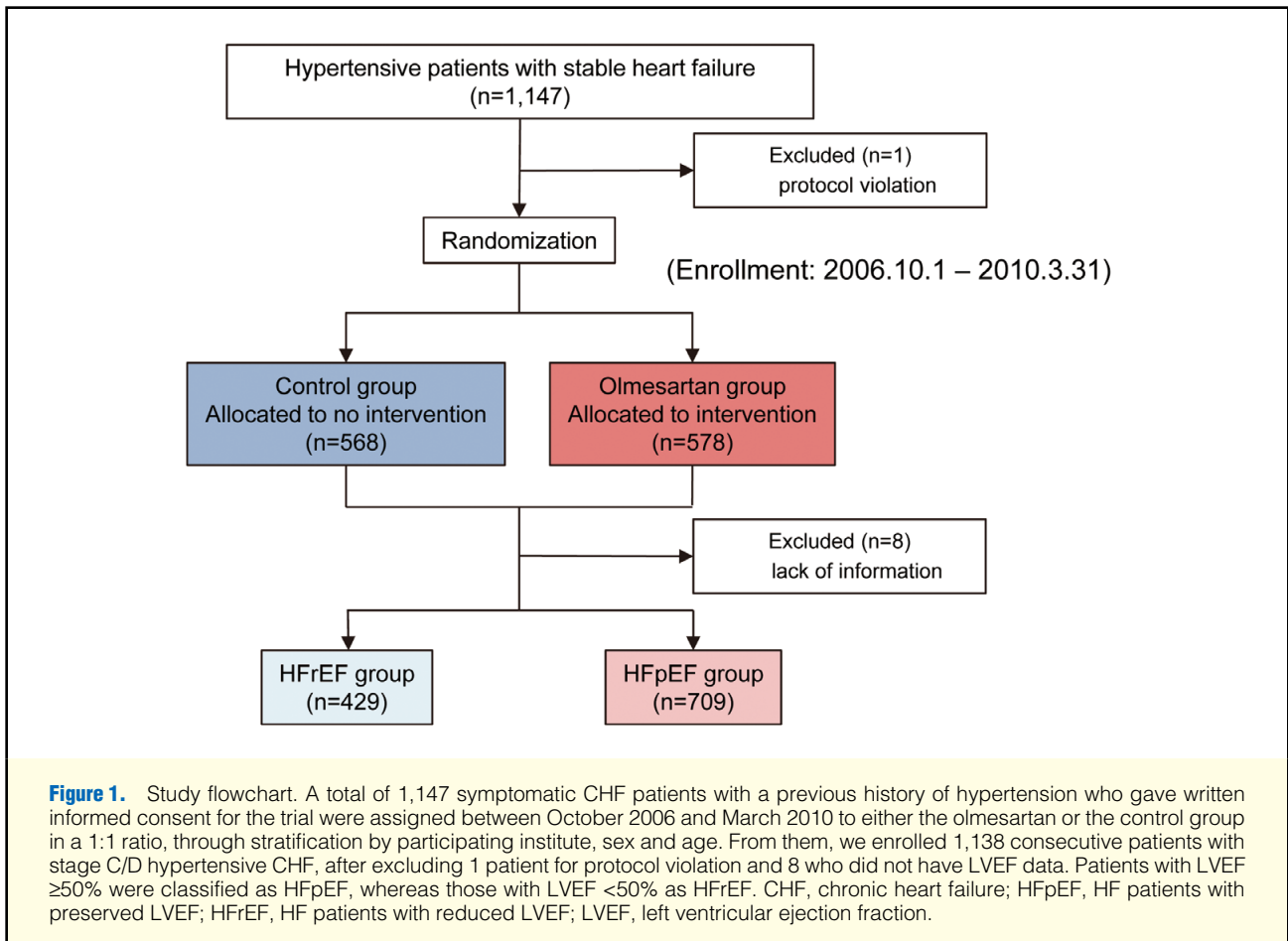
The SUPPORT Trial Investigators are listed in [Appendix S1](#).

Trial Registration: The SUPPORT Trial is registered at [clinicaltrials.gov/NCT00417222](http://clinicaltrials.gov/NCT00417222).

Mailing address: Hiroaki Shimokawa, MD, PhD, Professor and Chairman, Departments of Cardiovascular Medicine and Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan.  
E-mail: [shimo@cardio.med.tohoku.ac.jp](mailto:shimo@cardio.med.tohoku.ac.jp)

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Recent studies report that the prevalence of heart failure (HF) with preserved left ventricular ejection fraction (LVEF) (HFpEF) has been increasing worldwide.<sup>1-3</sup> Although guidelines recommend the use of  $\beta$ -blockers (BB) and renin-angiotensin system inhibitors (RASi), such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARB), and aldosterone receptor antagonists, to improve mortality and morbidity in HF patients with reduced EF (HFrEF), the guidelines merely recommend the use of diuretics to relieve symptoms and for adequate blood pressure control in HFpEF patients,<sup>4,5</sup> as there is no robust evidence of pharmacological interventions to improve mortality in HFpEF patients.<sup>6,7</sup>

In current HF management, combinations of evidence-based medications are commonly applied. However, it remains unclear whether the combination of RASi and BB is generally beneficial in HF patients, even those with HFrEF.<sup>8,9</sup> In the post-hoc analysis of the Valsartan Heart Failure Trial (Val-HeFT), triple combination therapy with valsartan, ACEI and BB was significantly associated with increased adverse effects on mortality and morbidity.<sup>8</sup> In contrast, the prospective Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Added Trial demonstrated that the addition of an ARB, candesartan, to ACEI was beneficial in patients with symptomatic CHF regardless of BB use.<sup>9</sup> We recently conducted the SUPPORT (Supplemental Benefit of Angiotensin Receptor Blocker in Hypertensive Patients with Stable Heart Failure Using Olmesartan) trial, demonstrating that the addi-

tion of olmesartan to ACEI and/or BB did not improve clinical outcomes but worsened renal function in hypertensive CHF.<sup>10,11</sup> The SUPPORT trial further demonstrated that the triple combination of olmesartan, ACEI and BB was associated with increased incidence of all-cause death, whereas the dual combination of olmesartan and BB was associated with reduced mortality.<sup>11</sup>

However, it remains to be elucidated whether LVEF influences the effects of additive use of ARB in the management of HF. This is clinically important from the viewpoint that the prevalence of HFpEF is increasing worldwide<sup>1-3</sup> and no therapeutic strategy has been established.<sup>4</sup> In the present study, we thus examined whether LVEF influences the effects of additive use of olmesartan in the management of CHF in the SUPPORT trial.

## Methods

### The SUPPORT Trial

The details of the SUPPORT trial have been described previously (NCT00417222).<sup>10,11</sup> Briefly, it was a prospective, randomized, open-label blinded endpoint (PROBE) study,<sup>10,11</sup> conducted according to the ethical principles of the Declaration of Helsinki and approved by the ethics committees of the 17 participating institutions in the Tohoku District of Japan (Appendix S1). The inclusion criteria of the present study were designed to enroll symptomatic CHF patients with hypertension aged 20–79 years who were treated with ACEI and/or

**Table 1. Baseline Characteristics of the Symptomatic CHF Patients With Hypertension**

	HF <sub>r</sub> EF			HF <sub>p</sub> EF		
	Control (n=218)	Olmesartan (n=211)	P value	Control (n=346)	Olmesartan (n=363)	P value
Age, years	64.9±10.8	64.6±10.7	0.792	65.9±9.7	66.5±10.1	0.454
Males, %	178 (81.7%)	172 (81.5%)	0.971	246 (71.1%)	255 (70.2%)	0.805
Body weight, kg	64.1±13.1	63.6±12.4	0.696	64.1±12.9	63.0±12.9	0.259
Body mass index, kg/m <sup>2</sup>	24.3±3.9	23.9±3.8	0.342	24.8±4.2	24.4±4.2	0.265
NYHA functional class			0.341			0.891
II	187 (88.6%)	202 (92.7%)		323 (93.4%)	342 (94.2%)	
III	23 (10.9%)	15 (6.9%)		22 (6.4%)	20 (5.5%)	
History of HF admission	133 (61.0%)	151 (71.6%)	0.021	153 (44.1%)	167 (52.2%)	0.609
IHD	103 (47.2%)	104 (49.3%)	0.700	156 (45.1%)	177 (48.8%)	0.329
Diabetes mellitus	102 (46.8%)	113 (53.6%)	0.177	186 (53.9%)	169 (46.6%)	0.060
Hemodynamics and LV function						
Systolic blood pressure, mmHg	122.4±18.5	123.7±19.0	0.488	130.1±17.1	131.5±17.1	0.274
Diastolic blood pressure, mmHg	71.7±11.2	73.8±13.5	0.090	75.2±11.7	75.3±11.4	0.935
Heart rate, beats/min	71.4±13.7	72.1±14.7	0.626	71.4±14.9	70.6±13.2	0.434
LVDd, mm	60.3±7.7	59.7±8.4	0.483	50.0±6.8	49.6±6.8	0.385
LVEF, %	38.7±8.1	38.6±8.4	0.898	63.1±8.6	63.8±8.8	0.272
Laboratory findings						
Hemoglobin, g/dl	13.7±2.0	14.1±1.7	0.024	13.8±1.8	13.7±1.7	0.573
Blood urea nitrogen, mg/dl	19.3±7.6	19.5±8.9	0.793	17.2±6.4	17.6±6.4	0.436
Creatinine, mg/dl	1.0±0.4	1.0±0.4	0.946	0.9±0.3	0.9±0.3	0.953
Serum sodium, mEq/L	141±2.6	141±2.8	0.140	141±2.5	142±2.2	0.042
Albumin, g/dl	4.1±0.5	4.2±0.4	0.006	4.2±0.4	4.2±0.4	0.577
LDL-C, mg/dl	108.3±30.1	107.3±30.6	0.735	106.6±30.1	108.9±31.1	0.358
eGFR, ml/min/1.73m <sup>2</sup>	63.2±21.9	62.1±19.2	0.588	66.0±19.3	65.3±18.1	0.620
BNP, pg/ml	122.0 (56.6, 237.8)	117.0 (55.5, 260.0)	0.750	58.7 (27.5, 139.0)	71.1 (30.2, 148.0)	0.280
Medication at baseline						
BB	172 (81.5%)	188 (86.2%)	0.183	227 (65.4%)	230 (63.4%)	0.567
ACEI	175 (82.9%)	184 (84.4%)	0.681	274 (79.0%)	290 (79.9%)	0.760
Diuretic	154 (70.6%)	161 (76.3%)	0.191	166 (48.0%)	166 (45.7%)	0.598
Loop diuretic	142 (65.1%)	142 (67.3%)	0.683	152 (43.9%)	149 (41.0%)	0.448
Spironolactone	76 (34.9%)	85 (40.3%)	0.273	76 (22.0%)	67 (18.5%)	0.262
Calcium-channel blocker	65 (29.8%)	55 (26.1%)	0.392	144 (41.6%)	166 (45.7%)	0.289
Statin	112 (51.4%)	111 (52.6%)	0.847	160 (46.2%)	175 (48.2%)	0.652

ACEI, angiotensin-converting enzyme inhibitor; BB,  $\beta$ -blocker; BNP, B-type natriuretic peptide; CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; HF<sub>p</sub>EF, HF patients with preserved LVEF; HF<sub>r</sub>EF, HF patients with reduced LVEF; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

BB.<sup>10,11</sup> The exclusion criteria were designed to exclude patients with substantive confounding medical conditions or an inability to meaningfully participate in the SUPPORT trial.<sup>10,11</sup> Finally, a total of 1,147 symptomatic CHF patients with a previous history of hypertension who gave written informed consent for the trial were assigned to either the olmesartan or the control group in a 1:1 ratio, through stratification by participating institute, sex and age between October 2006 and March 2010. The patients were followed until March 31, 2013. Olmesartan was initiated at a dose of 5–10 mg/day, and attending physicians were encouraged to up-titrate it to 40 mg/day whenever possible in the olmesartan group, but no ARB use was allowed in the control group. The diagnosis of CHF was made based on the Framingham criteria<sup>12</sup> by an attending physician(s) at each hospital. All physicians were encouraged to control the blood pressure of the patients in each group according to the recommendations of the JNC7.<sup>13</sup>

### Study Design

From among 1,147 patients in the SUPPORT trial, we enrolled 1,138 consecutive patients with stage C/D hypertensive CHF in the present study, after excluding 1 patient for protocol violation and 8 who did not have LVEF data (Figure 1). We divided them into HF<sub>p</sub>EF and HF<sub>r</sub>EF based on LVEF levels measured by echocardiography at the time of enrollment at each hospital. In the present study, patients with LVEF  $\geq 50\%$  were classified as HF<sub>p</sub>EF, and those with LVEF  $< 50\%$  as HF<sub>r</sub>EF.<sup>4</sup> The primary endpoint of the present study was all-cause death and the secondary endpoint was worsening renal function (WRF).<sup>10,11</sup> WRF was defined as an increase in serum creatinine level  $> 2$ -fold from the baseline at any time point during the follow-up period.<sup>14</sup> To evaluate WRF, we further evaluated changes in the urinary albumin to creatinine ratio (UACR)<sup>15</sup> during the follow-up period. Urine samples were collected in outpatient clinics or before discharge, and were

transferred to the central laboratory (SRL, Inc, Tokyo, Japan) to calculate the UACR.

### Statistical Analysis

The primary and secondary endpoints were analyzed based on the time to the first occurrence, according to the intention-to-treat principle, including all patients lost to follow-up and censored at the day of the last contact. Survival curves were estimated using the Kaplan-Meier method and compared with a 2-sided log-rank test. The effects of olmesartan were examined using Cox proportional hazards models. Subgroup analyses were performed according to baseline medications and other clinical parameters. Continuous variables are presented as mean±standard deviation except for B-type natriuretic peptide (BNP). BNP levels are presented as median and interquartile range. Categorical variables are presented as number and percentage. Group comparisons were made with the Mann-Whitney test for continuous variables, and the chi-squared test without continuity correction for categorical variables. For statistical analysis of longitudinal change in the logarithm of (UACR+1), a linear mixed-effect model (LMEM)<sup>16</sup> was utilized. The LMEM was fitted with the random intercept for each patient and the trend in duration as the fixed effect, using the nlme package of R. All statistical analyses were performed using IBM SPSS Statistics 21.0 (IBM, Somers, NY, USA) and R 3.0.2 (R Foundation for Statistical Computing, Vienna. <http://www.R-project.org/>). Two-sided probability values <0.05 and P values for interaction <0.1 were considered to be statistically significant.

## Results

### Patients Characteristics

In the HFrEF patients (mean LVEF, 38%), baseline characteristics were almost comparable between the olmesartan and control groups except for history of admission for HF and serum hemoglobin and albumin levels (Table 1). The mean age was 64 years and 82% were male. The prevalence of ischemic heart disease (IHD) was 48%. ACEIs and BB were prescribed in 84% and 84%, respectively, and 68% were treated with both drugs.

In the HFpEF patients (mean LVEF, 63%), baseline characteristics were comparable between the olmesartan and control groups except for serum sodium level (Table 1). The mean age was 66 years and 71% were male. The prevalence of IHD was 47%. ACEIs and BB were prescribed in 80% and 64%, respectively, and 45% were treated with both drugs.

### Additive Effects of Olmesartan on Mortality in HFrEF and HFpEF Patients

All-cause death occurred in 39 and 55 patients in the control and olmesartan groups, respectively, of HFrEF patients, and in 46 and 43 patients in the control and olmesartan groups, respectively of HFpEF patients (P for interaction, 0.07) (Figure 2A). In the patients treated with both ACEI and BB, the addition of olmesartan was significantly associated with increased incidence of all-cause death in HFrEF, but not in HFpEF patients (P for interaction, 0.02) (Figure 2B). Importantly, in HFrEF patients, the addition of olmesartan to the combination of ACEI and BB was associated with increased mortality regardless of the presence or absence of IHD (P for interaction, 0.835), and it tended to be associated with decreased mortality in HFpEF patients with IHD, with a significant interaction vs. HFpEF patients without IHD (P for interaction, 0.057) (Table S1). In the patients treated with ACEI but not BB, the

addition of olmesartan was not associated with reduced incidence of all-cause death in either HFrEF or HFpEF patients (P for interaction vs. HFpEF, 0.22) (Figure 2C), regardless of the presence or absence of IHD (P for interaction, 0.527 and 0.173 for HFrEF and HFpEF patients, respectively) (Table S1).

In contrast, in the patients treated with BB but not an ACEI, the addition of olmesartan was significantly associated with reduced incidence of all-cause death in HFpEF patients, but not in HFrEF patients (P for interaction, 0.52) (Figure 2D). Of note, however, the combination of olmesartan and BB tended to be associated with decreased mortality in HFrEF patients with IHD, with a significant interaction vs. those without IHD (P for interaction, 0.091), whereas the effect of combination use of olmesartan and BB was comparable between HFpEF patients with and without IHD (P for interaction, 0.531) (Table S1).

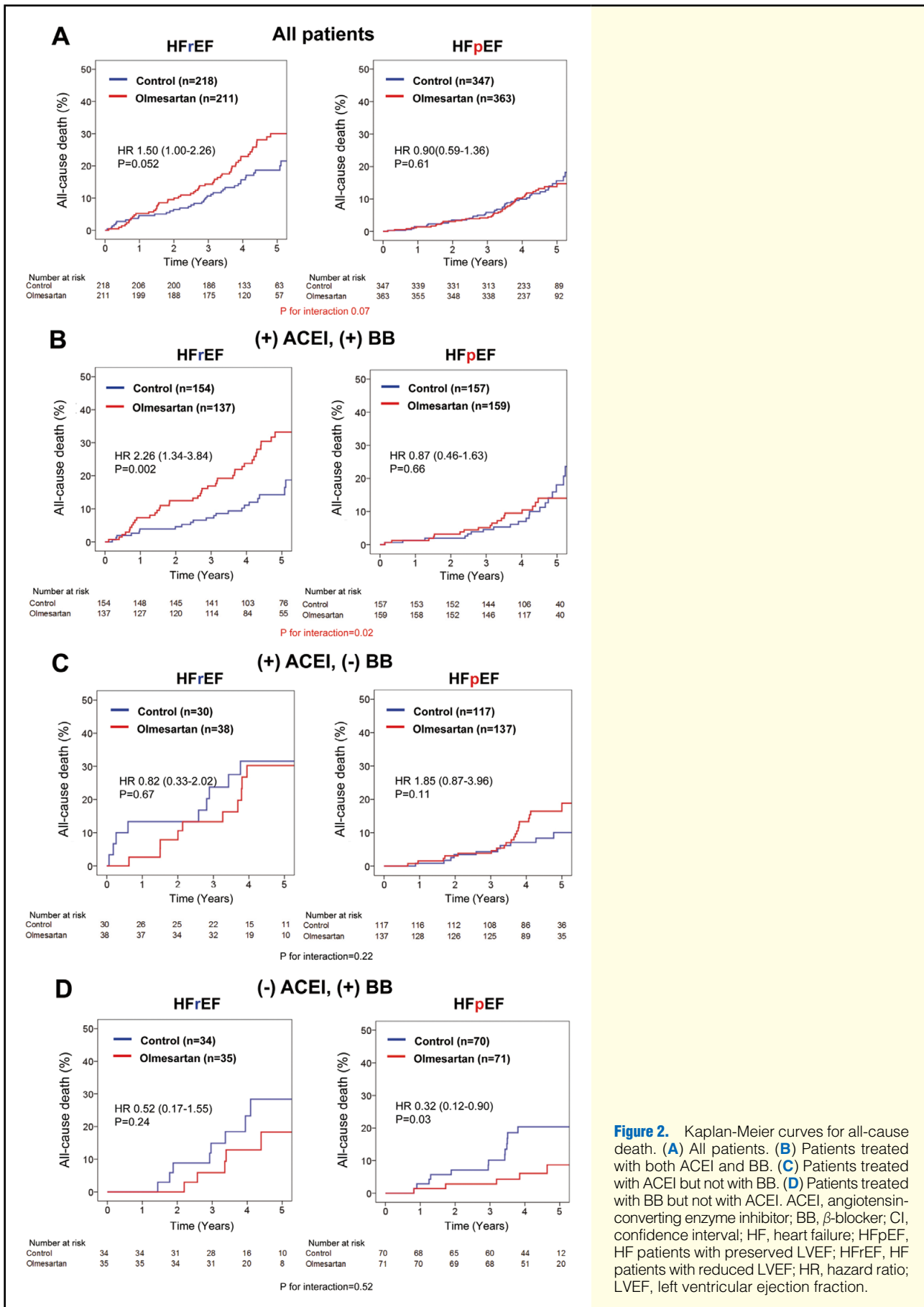
### Additive Effect of Olmesartan on WRF in HFrEF and HFpEF Patients

WRF occurred in 31 patients (14.2%) in the control group and in 42 (19.9%) in the olmesartan group of HFrEF patients (P=0.09), and in 30 (8.6%) patients in the control group and 54 (14.9%) in the olmesartan group of HFpEF patients (P=0.01) (P for interaction, 0.70) (Figure 3A). In the patients treated with both ACEI and BB, the addition of olmesartan tended to be associated with increased WRF in HFpEF patients (P=0.09), and was significantly associated with increased incidence of WRF in HFrEF patients (P=0.01) (P for interaction, 0.55) (Figure 3B). In patients treated with an ACEI but not BB, the addition of olmesartan was associated with increased WRF in HFpEF patients (P=0.02), but not in HFrEF patients (P=0.63) (P for interaction, 0.09) (Figure 3C). Interestingly, in the patients treated with BB but without an ACEI, the addition of olmesartan was not associated with increased incidence of WRF in either HFpEF (P=0.92) or HFrEF (P=0.61) patients (P for interaction, 0.69) (Figure 3D).

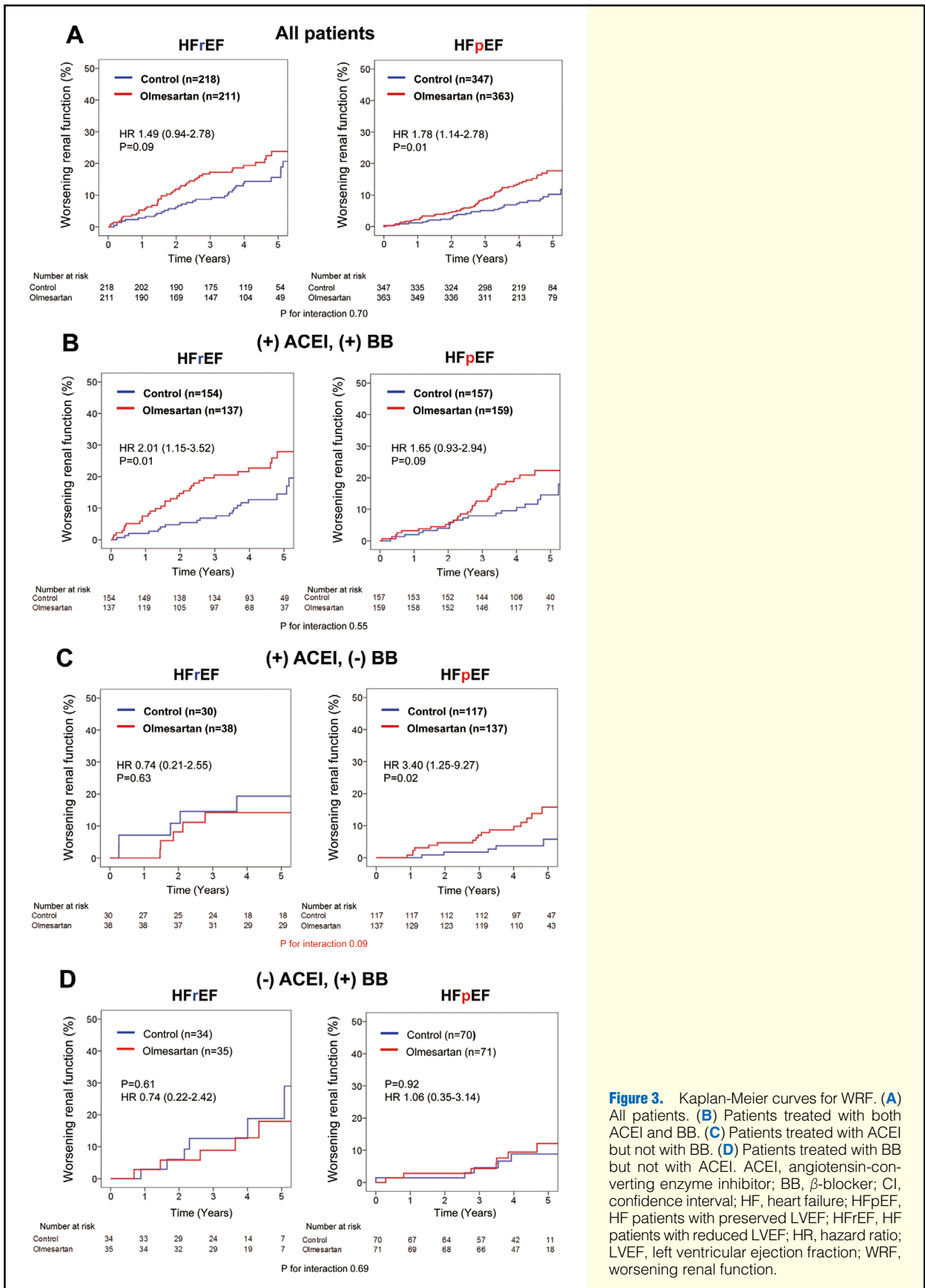
UACR was increased in HFrEF patients during the follow-up period regardless of the addition of olmesartan, but was unaltered in HFpEF patients treated with the addition of olmesartan (Figure 4A). In the patients treated with both ACEI and BB, UACR was increased in HFrEF patients regardless of the addition of olmesartan, but not in HFpEF patients (Figure 4B). In the patients treated with ACEI but without BB, UACR was unaltered in both HFrEF and HFpEF patients regardless of the addition of olmesartan (Figure 4C). In contrast, in the patients treated with BB but without ACEI, UACR was increased in both HFrEF and HFpEF patients when olmesartan was not added, but it was unaltered in both groups when olmesartan was added (Figure 4D). Table 2 shows the rearrangement of drug combinations in a descending manner in terms of the slope of UACR changes during the follow-up period. In HFrEF patients, not only the single use of BB, but also the dual combination use of ACEI and BB and the triple combination of olmesartan, ACEI and BB were significantly associated with an increase in the UACR, whereas the dual combination of olmesartan and BB was not. On the other hand, in HFpEF patients, none of the drug combinations, except the single use of BB, was significantly associated with UACR increase.

## Discussion

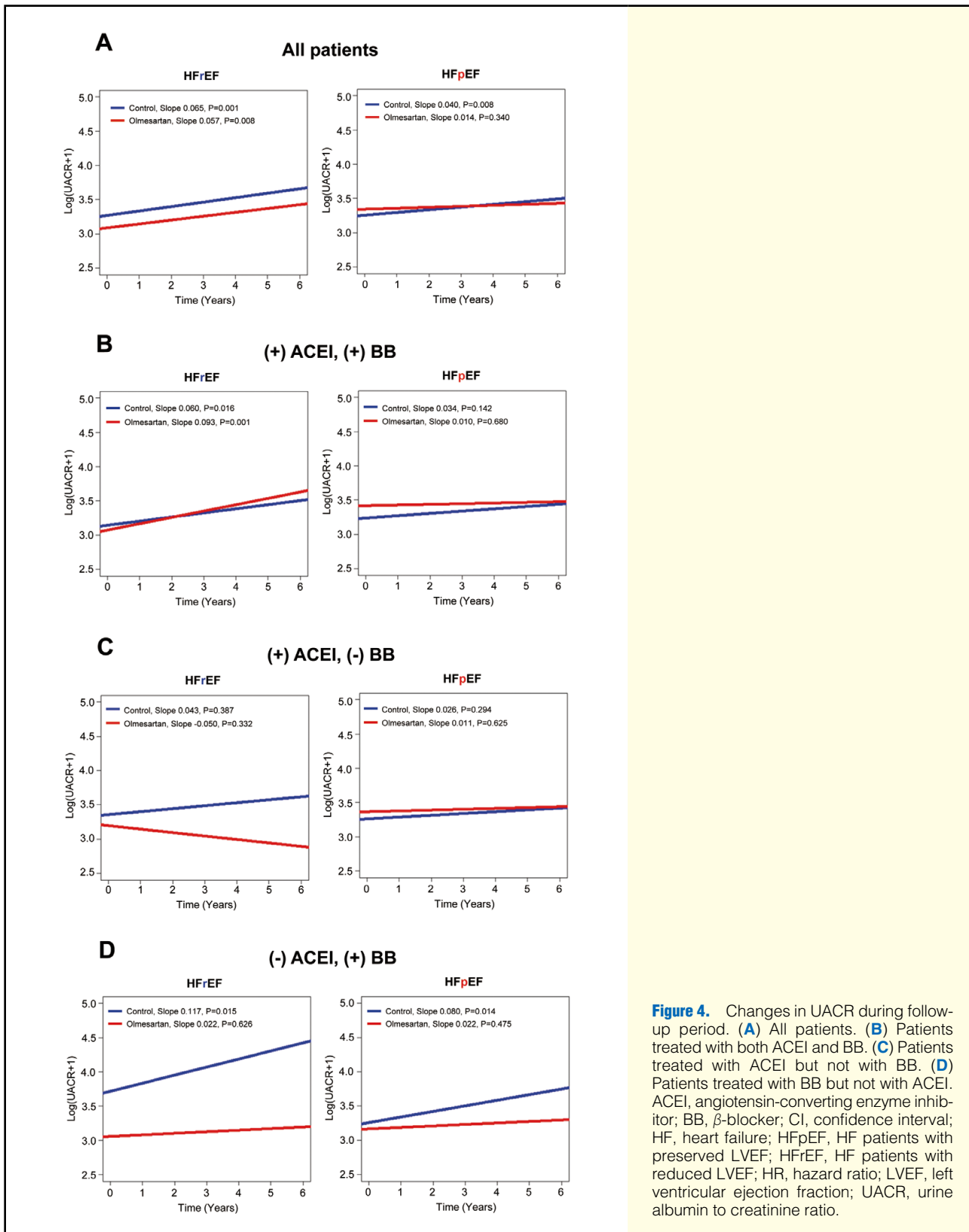
In the present substudy of the SUPPORT trial, we examined whether additive treatment with an ARB, olmesartan, reduced the mortality and morbidity of CHF patients with a history of hypertension treated with ACEI and/or BB with special refer-



**Figure 2.** Kaplan-Meier curves for all-cause death. (A) All patients. (B) Patients treated with both ACEI and BB. (C) Patients treated with ACEI but not with BB. (D) Patients treated with BB but not with ACEI. ACEI, angiotensin-converting enzyme inhibitor; BB,  $\beta$ -blocker; CI, confidence interval; HF, heart failure; HF<sub>p</sub>EF, HF patients with preserved LVEF; HF<sub>r</sub>EF, HF patients with reduced LVEF; HR, hazard ratio; LVEF, left ventricular ejection fraction.



**Figure 3.** Kaplan-Meier curves for WRF. (A) All patients. (B) Patients treated with both ACEI and BB. (C) Patients treated with ACEI but not with BB. (D) Patients treated with BB but not with ACEI. ACEI, angiotensin-converting enzyme inhibitor; BB,  $\beta$ -blocker; CI, confidence interval; HF, heart failure; HF<sub>p</sub>EF, HF patients with preserved LVEF; HF<sub>r</sub>EF, HF patients with reduced LVEF; HR, hazard ratio; LVEF, left ventricular ejection fraction; WRF, worsening renal function.



**Figure 4.** Changes in UACR during follow-up period. (A) All patients. (B) Patients treated with both ACEI and BB. (C) Patients treated with ACEI but not with BB. (D) Patients treated with BB but not with ACEI. ACEI, angiotensin-converting enzyme inhibitor; BB,  $\beta$ -blocker; CI, confidence interval; HF, heart failure; HFpEF, HF patients with preserved LVEF; HFReF, HF patients with reduced LVEF; HR, hazard ratio; LVEF, left ventricular ejection fraction; UACR, urine albumin to creatinine ratio.

ence to LVEF. In HFpEF patients, the addition of olmesartan to BB was associated with improved mortality rate without developing WRF. On the other hand, the triple combination of olmesartan, ACEI and BB was associated with increased inci-

dence of death and WRF in HFReF patients. These results may provide us with important information on the use of ARBs in the management of CHF.

Table 2. Trends in UACR During Follow-up				
Olmesartan	ACEI	BB	Slope	P value
<b>HFrEF</b>				
-	-	+	0.117	0.015
+	+	+	0.093	0.001
-	+	+	0.060	0.016
-	+	-	0.043	0.387
+	-	+	0.022	0.626
+	+	-	-0.050	0.332
<b>HFpEF</b>				
-	-	+	0.080	0.014
-	+	+	0.034	0.142
-	+	-	0.026	0.294
+	-	+	0.022	0.475
+	+	-	0.011	0.625
+	+	+	0.010	0.680

Drug combinations are arranged in descending order in terms of the slope value in both HFrEF and HFpEF patients. UACR, urine albumin to creatinine ratio. Other abbreviations as in Table 1.

### Combination Use of RASI and BB in Hypertensive HFpEF Patients

In the present study, we demonstrated that the addition of olmesartan to BB therapy was associated with reduced mortality rate without development of WRF in HFpEF patients, but to the combination of ACEI and BB or to ACEI alone it was not. To the best of our knowledge, this is the first study to demonstrate a clinical benefit of drug combination in HFpEF patients. HFpEF patients, as compared with HFrEF patients, are characterized by their older age and higher prevalence of female sex and hypertension.<sup>4</sup> Among them, hypertension has been implicated in a central role in the pathogenesis of HFpEF.<sup>17</sup> Thus, management of blood pressure is crucial in HFpEF patients, especially in those with hypertension. Indeed, clinical guidelines simply recommend adequate control of systolic and diastolic blood pressures in HFpEF patients without specifying any type of antihypertensive medication.<sup>4,5</sup> In the present study, however, control of blood pressure during the follow-up period were comparable among the subgroups based on the combination of medications (Figure S1). Thus, factor(s) other than blood pressure control could explain why the combined use of olmesartan and BB was associated with improved mortality rates in HFpEF patients in the present study.

However, it should be noted that the present result that a combination of olmesartan and BB was associated with reduced mortality in HFpEF patients was not consistent with the J-DHF, which found no beneficial effect of carvedilol in patients with diastolic HF regardless of treatment with ACEI or ARB.<sup>18</sup> This discrepancy could be explained by differences in the baseline characteristics of the patients in the J-DHF and the SUPPORT trial, such as age (72.0 vs. 65.7 years), prevalence of males (58.4% vs. 75.0%) and BNP levels (227 vs. 143 pg/ml), in addition to differences in study design such as the definition of HF (diastolic dysfunction vs. HFpEF), and the BB used (carvedilol vs. any BB) and ARB (any ARB vs. olmesartan). However, it should be noted that the baseline characteristics of the present patients, characterized by relatively younger age, higher prevalence of males and stable HF status with low BNP levels, were similar to those of the HFpEF patients in the CHARM-Preserved study, which demonstrated a benefit of candesartan for HFpEF.<sup>7</sup> Furthermore, a subanalysis

of the I-PRESERVE Study demonstrated that irbesartan was effective in patients with lower NT-proBNP levels but not in those with higher NT-proBNP levels.<sup>19</sup> These lines of evidence suggest that ARBs are beneficial for relatively younger patient populations and/or in the early stage of HFpEF, although the underlying mechanism is unclear.

It has been reported that olmesartan has beneficial effects on glucose metabolism, insulin resistance, and lipid metabolism,<sup>20</sup> and that olmesartan significantly reduced vascular inflammation in patients with essential hypertension.<sup>21</sup> Because the inflammatory state, including endothelial dysfunction and increased oxidative stress, is considered as one of the central pathophysiological aspects of HFpEF,<sup>22</sup> these anti-inflammatory and anti-metabolic effects of olmesartan could be beneficial for HFpEF patients. On the other hand, it has been also reported that BB have beneficial effects in hypertensive HFpEF patients because they improve hypertension, and LV filling and thus reduce heart rate and myocardial oxygen demand.<sup>23</sup> However, although a meta-analysis showed that RASI decreased HF hospitalizations<sup>24</sup> and a propensity score-matched cohort study showed that use of RASI was associated with improved mortality rates,<sup>25</sup> previous RCTs failed to show beneficial effects of RASI to improve the mortality or morbidity of HFpEF patients.<sup>6,7</sup> Similarly, although a meta-analysis<sup>26</sup> and a propensity score-matched cohort study<sup>23</sup> suggested improved outcomes in HFpEF patients treated with BB, previous RCTs<sup>18,27</sup> failed to find a benefit of BB for improved outcomes. These lines of evidence are the reasons why the current guidelines do not recommend routine use of RASI or BB for the control of blood pressure in HFpEF patients.<sup>4,5</sup> Thus, it is conceivable that the beneficial effects of olmesartan and BB alone are not strong enough alone to counteract these other factors, but when combined, olmesartan and BB may have synergistic effects that show beneficial cardioprotective actions in HFpEF patients.

### Combination Use of RASI and BB in Hypertensive HFrEF Patients

In the present study, more than 80% of HFrEF patients were treated with both ACEI and BB before randomization. However, the addition of olmesartan was significantly associated with poor prognosis and WRF in these patients. Indeed, the benefit of the triple combination of ACEI, ARB and BB remains controversial.<sup>8,9</sup> The Val-HeFT trial showed that valsartan use was associated with increased adverse effects on mortality and morbidity in the subgroup receiving both an ACEI and BB,<sup>8</sup> a similar finding in the HFrEF patients of the present study. On the other hand, the CHARM-Added trial showed that the addition of an ARB, candesartan, was beneficial in symptomatic CHF patients being treated with an ACEI and BB.<sup>9</sup> Although the precise mechanism of the discrepancy in effectiveness of the triple combination therapy between the Val-HeFT and the CHARM-added trials is unclear, it could be explained by differences in the patients' backgrounds; the majority of the patients in the Val-HeFT trial were in NYHA class II (62%), whereas those in the CHARM-added Trial were in NYHA class III (73%), although LVEF levels were comparable between the 2 trials (27% vs. 28%, respectively). In our SUPPORT trial, the majority of the HFrEF patients (91%) were in NYHA class II. Thus, the effect of the triple combination of ARB, ACEI and BB may differ according to the severity of HF in HFrEF patients, and routine application of the triple combination should be avoided in hypertensive patients with HFrEF. In the present study, the combination of olmesartan and BB was associated with improved mortality rates in HFpEF patients, but not in HFrEF patients. However, this



discrepancy between HFpEF and HFrfEF patients could be explained by the relatively small number of patients with BB alone at baseline in the HFrfEF group, as the addition of olmesartan tended to be associated with reduced mortality in HFrfEF patients without a significant interaction vs. HFpEF patients. Thus, the present results may not deny the beneficial effects of combined use of BB and olmesartan in HFrfEF patients. In particular, the combination of olmesartan and BB tended to be associated with better prognosis in HFrfEF patients with IHD compared with those without it. It is conceivable that the difference in the prognostic effect of the dual combination of olmesartan and BB between the HFrfEF patients with and without IHD could be explained, at least in part, by the beneficial effect of olmesartan in reducing coronary atheroma progression.<sup>28</sup>

### Renal Protective Effects of Olmesartan and BB

In the present study, although the addition of olmesartan to the combination of ACEI and BB was associated with an increase in WRF in HFrfEF patients and tended to be so in HFpEF patients, that to BB alone was not associated with increased WRF in either HFrfEF or HFpEF patients. The RAS is considered essential for preserving renal function and glomerular filtration.<sup>29</sup> Renal perfusion pressure is a major determinant of glomerular hydraulic filtration pressure.<sup>29</sup> The kidney responds to a decrease in blood supply by increasing renin and angiotensin in order to maintain its function and glomerular filtration within the normal range, which is known as the nephrocentric reaction.<sup>29</sup> In CHF patients, renal perfusion usually reduces along with a decrease in cardiac output, followed by activation of the RAS to maintain renal function. Thus, excessive blockade of the RAS by the combination of olmesartan and ACEI without BB in HFpEF patients might have resulted in decreased renal perfusion and subsequent WRF in the present study.

We recently reported that increased albuminuria, when evaluated by urine dipstick test, predicted the mortality risk of HFpEF patients regardless of glomerular filtration ratio levels.<sup>30</sup> In the present study, albuminuria, a marker of glomerular damage,<sup>15</sup> was not increased during the follow-up period in HFpEF patients when BB were combined with olmesartan, ACEI or both, but was significantly increased when not combined with RAS inhibitors. In contrast, in the HFrfEF patients, use of BB was generally associated with an increase in albuminuria except for combined use with olmesartan but not with ACEI. Because albuminuria is caused by activation of the RAS and/or sympathetic nervous system, as well as by inflammation,<sup>15,30</sup> combined use of RASI and BB may be ideal to reduce albuminuria. Thus, from the viewpoint of renal protection, the present results suggest that the combination of olmesartan and BB could be beneficial in hypertensive CHF patients.

### Study Limitations

Several limitations should be mentioned. First, because the SUPPORT trial was conducted in an open-label fashion, caution is warranted when interpreting the present results. Second, it should be noted that the patients enrolled in the SUPPORT trial had relatively well-controlled blood pressure and were only mildly symptomatic before randomization as compared with previous HF trials. Third, we did not take into consideration information about the dose of olmesartan, ACEIs or BB. Fourth, no detailed information on diastolic dysfunction other than LVEF was available. Fifth, because the present populations of both HFrfEF and HFpEF were small, further studies with a large sample size are needed to confirm the

present findings. Sixth, the possible influence of the Great East Japan Earthquake in 2011 in the Tohoku area should be considered,<sup>31</sup> because it occurred after the randomization and during the follow-up period of the present study. However, because the results remained unaltered even after exclusion of results from hospitals located in the area with severe damage (data not shown), the influence of the earthquake may be minimal.

### Conclusions

The present subanalysis of the SUPPORT trial suggests that the combination of olmesartan and BB is beneficial for hypertensive patients with HFpEF, whereas the triple combination therapy of olmesartan, ACEI and BB is harmful for those with HFrfEF.

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## Supplementary Files

### Supplementary File 1

#### Appendix S1. SUPPORT Trial Investigators

**Table S1.** Effect of olmesartan on all-cause death according to the presence or absence of IHD

**Figure S1.** Time course in blood pressure values presented as mean  $\pm$  standard deviation.

Please find supplementary file(s);  
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