Clinical impacts of additive use of olmesartan in hypertensive patients with chronic heart failure: the supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial

Yasuhiko Sakata[1], Nobuyuki Shiba[2], Jun Takahashi[1], Satoshi Miyata[3], Kotaro Nochioka[1], Masanobu Miura[1], Tsuyoshi Takada[2], Chiharu Saga[1], Tsuyoshi Shinozaki[4], Masafumi Sugi[5], Makoto Nakagawa[6], Nobuyo Sekiguchi[7], Tatsuya Komaru[8], Atsushi Kato[9], Mitsumasa Fukuchi[10], Eiji Nozaki[11], Tetsuya Hiramoto[12], Kanichi Inoue[13], Toshikazu Goto[14], Masatoshi Ohe[15], Kenji Tamaki[16], Setsuro Ibayashi[17], Nobumasa Ishide[18], Yukio Maruyama[19], Ichiro Tsuji[20], and Hiroaki Shimokawa[1,3]*, on Behalf of the SUPPORT Trial Investigators[†]

[1]Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan; [2]Department of Cardiovascular Medicine, International University of Health and Welfare Hospital, Nasushiobara, Japan; [3]Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan; [4]Cardiovascular Division, Sendai Medical Center, National Hospital Organization, Sendai, Japan; [5]Cardiovascular Division, Iwaki Kyouritsu Hospital, Iwaki, Japan; [6]Department of Cardiology, Iwate Prefectural Isawa Hospital, Oshu, Japan; [7]Cardiovascular Division, Hiraka General Hospital, Yokote, Japan; [8]Department of Cardiology, Miyagi Cardiovascular and Respiratory Center, Kurihara, Japan; [9]Cardiovascular Division, Sendai Open Hospital, Sendai, Japan; [10]Cardiovascular Division, Sendai Tokushukai Hospital, Sendai, Japan; [11]Department of Cardiology, Iwate Prefectural Central Hospital, Morioka, Japan; [12]Cardiovascular Division, Osaki Citizen Hospital, Osaki, Japan; [13]Cardiovascular Division, South Miyagi Medical Center, Ogawara, Japan; [14]Department of Cardiology, Yamagata Prefectural Central Hospital, Yamagata, Japan; [15]Cardiovascular Division, Kojirakawa Shiseido Hospital, Yamagata, Japan; [16]Department of Cardiology, Iwate Prefectural Miyako Hospital, Miyako, Japan; [17]Seiai Rehabilitation Hospital, Onojo, Japan; [18]Sendai Shirayuri Women's College, Sendai, Japan; [19]Hoshi General Hospital, Koriyama, Japan; and [20]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

We examined whether an additive treatment with an angiotensin receptor blocker, olmesartan, reduces the mortality and morbidity in hypertensive patients with chronic heart failure (CHF) treated with angiotensin-converting enzyme (ACE) inhibitors, β-blockers, or both. In this prospective, randomized, open-label, blinded endpoint study, a total of 1147 hypertensive patients with symptomatic CHF (mean age 66 years, 75% male) were randomized to the addition of olmesartan ($n = 578$) to baseline therapy vs. control ($n = 569$). The primary endpoint was a composite of all-cause death, non-fatal acute myocardial infarction, non-fatal stroke, and hospitalization for worsening heart failure. During a median follow-up of 4.4 years, the primary endpoint occurred in 192 patients (33.2%) in the olmesartan group and in 166 patients (29.2%) in the control group [hazard ratio (HR) 1.18; 95% confidence interval (CI), 0.96–1.46, $P = 0.112$], while renal dysfunction developed more frequently in the olmesartan group (16.8 vs. 10.7%, HR 1.64; 95% CI 1.19–2.26, $P = 0.003$). Subgroup analysis revealed that addition of olmesartan to combination of ACE inhibitors and β-blockers was associated with increased incidence of the primary endpoint (38.1 vs. 28.2%, HR 1.47; 95% CI 1.11–1.95, $P = 0.006$), all-cause death (19.4 vs. 13.5%, HR 1.50; 95% CI 1.01–2.23, $P = 0.046$), and renal dysfunction (21.1 vs. 12.5%, HR

Figure 1 Trial profile.

Interim analysis and data monitoring

Meetings of the Data Safety Monitoring Board, which is independent of the study committees, were held twice a year throughout the trial period to monitor the study safety until the end of the trial. Interim analyses were conducted at the end of and 2 years after the end of the registration period, namely March 2010 and September 2011, to evaluate the primary endpoint and the safety for the continuation of the trial.

Statistical analysis

All analyses were performed according to a predefined statistical analysis plan. Y.S., S.M., and H.S. had a full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis. The primary and secondary endpoints were analysed based on the time to the first occurrence, according to the intention-to-treat principle, including all patients of lost to follow-up censored at the day of the last contact. Survival curves were estimated using the Kaplan–Meier procedure and compared with a two-sided log-rank test. Based on the results of the CHART-1 Study,[14,15] we assumed that the annual incidence of the primary composite endpoint would be ~12% in the SUPPORT trial and thus 480 patients would be required on the condition of 3-year follow-up for each arm to provide 80% power to detect 30% risk reduction by olmesartan, using a two-sided significance level of 0.05 by the log-rank test.[11] Considering that ~15% of cases would be lost during follow-up or unsuitable for analysis, we estimated that >565 patients in each group (control and olmesartan) would be needed to complete the trial.

The P-value of the interim analysis was 0.005 while the P-value of the final analysis was 0.048. The effects of olmesartan were examined using Cox proportional hazards models. Subgroup analyses were performed according to baseline medication and other baseline characteristics and clinical parameters. Continuous variables are presented as means ± standard deviations except brain natriuretic peptide (BNP). Brain natriuretic peptide levels are presented as medians and interquartile ranges. Categorical variables were presented as numerals and percentages. Group comparisons were made with the Mann–Whitney test for continuous variables, and the χ^2-test without continuity correction for categorical variables. 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/). A two-sided probability values of <0.05 and P-values for interaction <0.1 were considered to be statistically significant.

Results

Patient characteristics

Baseline characteristics were comparable between the olmesartan and the control groups (*Table 2*). The mean age was 66 and 75% of the patients were male. Functional class of HF was in NYHA Class II in 93% and Class III in 7%, and underlying heart disease included ischaemic heart disease in 48% and dilated cardiomyopathy in 21%. Mean systolic/diastolic blood pressure was 128/74 mmHg, and mean left ventricular ejection fraction (LVEF) was 54%. At the time of randomization, ACE inhibitors and β-blockers were prescribed in 81 and 72% of the patients, respectively.

Drug adherence and blood pressure

At the time of randomization, systolic/diastolic blood pressure was 128.7/74.8 ± 18.2/12.2 and 127.1/73.8 ± 18.1/11.7 mmHg in the

Table 2   **Baseline characteristics**

	Control (*n* = 569)	Olmesartan (*n* = 578)	*P*-value
Age (years)	65.5 ± 10.1	65.8 ± 10.4	0.445
Males (%)	427 (75.2%)	429 (74.2%)	0.71
Body weight (kg)	64.1 ± 12.9	63.2 ± 12.7	0.297
Height (cm)	161.0 ± 9.1	160.8 ± 9.6	0.655
Body mass index (kg/m^2)	24.6 ± 4.1	24.2 ± 4.1	0.185
NYHA functional class			0.564
II	530 (93.5%)	535 (92.6%)	
III	37 (6.5%)	43 (7.4%)	
Baseline cardiovascular disease			
Ischaemic heart disease	262 (46.1%)	283 (49%)	0.337
Dilated cardiomyopathy	132 (23.2%)	110 (19%)	0.081
Diabetes mellitus	292 (51.4%)	283 (49%)	0.408
Haemodynamics and LV function			
Systolic blood pressure (mmHg)	127.1 ± 18.0	128.7 ± 18.2	0.081
Diastolic blood pressure (mmHg)	73.9 ± 11.7	74.8 ± 12.2	0.311
Heart rate (bpm)	71.5 ± 14.6	71.2 ± 13.8	0.808
LVDd (mm)	54.0 ± 8.7	53.3 ± 9.0	0.113
LVEF (%)	53.7 ± 14.5	54.5 ± 14.9	0.277
≤40%	106 (18.8%)	110 (19.2%)	0.874
>40 and <50%	112 (19.9%)	101 (17.6%)	0.328
≥50%	346 (61.3%)	363 (63.2%)	0.510
Laboratory findings			
Haemoglobin (g/dL)	13.7 ± 1.9	13.8 ± 1.7	0.279
Blood urea nitrogen (mg/dL)	18.0 ± 6.9	18.3 ± 7.5	0.556
Creatinine (mg/dL)	0.95 ± 0.36	0.94 ± 0.33	0.956
Albumin (mg/dL)	4.2 ± 0.4	4.2 ± 0.4	0.28
LDL-C (mg/dL)	107.3 ± 30.0	108.2 ± 30.8	0.775
eGFR (mL/min/1.73 m^2)	70.4 ± 24.4	70.0 ± 22.6	0.887
BNP (pg/mL)	78.2 (37.8, 173.0)	84.2 (36.7, 188.8)	0.63
Baseline medication			
β-Blocker	416 (73.2%)	405 (70.1%)	0.234
ACEI	460 (81.0%)	469 (81.1%)	0.946
Diuretics	322 (56.7%)	328 (56.7%)	0.984
Thiazides	22 (3.9%)	19 (3.3%)	0.593
Loop diuretics	296 (52.1%)	292 (50.5%)	0.589
Spironolactone	153 (26.9%)	152 (26.3%)	0.807
Calcium-channel blocker	212 (37.3%)	222 (38.4%)	0.705
Statin	274 (48.2%)	287 (49.7%)	0.632

NYHA, New York Heart Association; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide.

olmesartan and the control group, respectively (*P* = 0.081/0.311). Changes in systolic/diastolic blood pressure in both groups are shown in *Figure 2*. There was no significant difference in systolic/diastolic blood pressure at any point between the two groups.

In the olmesartan group, olmesartan was not prescribed in 18 (3.1%), 56 (9.4%), 70 (12.1%), 65 (11.2%), 48 (10.7%), 19 (9.7%), and 1 (4.5%) patients at 0, 1, 2, 3, 4, 5, and 6 years after randomization, respectively. In the control group, the cumulative incidence of any ARB use was none (0%), 2 (0.3%), 4 (0.7%), 8 (1.4%), 8 (1.4%), 8 (1.4%), and 8 (1.4%) at 0, 1, 2, 3, 4, 5, and 6 years after randomization, respectively. In the olmesartan group, mean dose of olmesartan (mg/day) at 0, 1, 2, 3, 4, 5, and 6 years after randomization was 9.5, 13.3, 15.4, 16.1, 17.4, 17.9, and 16.5, respectively.

When the primary endpoint occurred or the SUPPORT trial ended, 58 patients (10.0%) were not taking olmesartan in the olmesartan group, whereas four patients (0.7%) were taking ARB in the

Figure 2 Time course in blood pressure. Blood pressure values are presented as mean $\pm$ standard deviations. There were no statistical differences in systolic or diastolic blood pressure at each point between the olmesartan and the control groups.

Figure 3 Kaplan−Meier curves for the primary endpoint for overall patients.
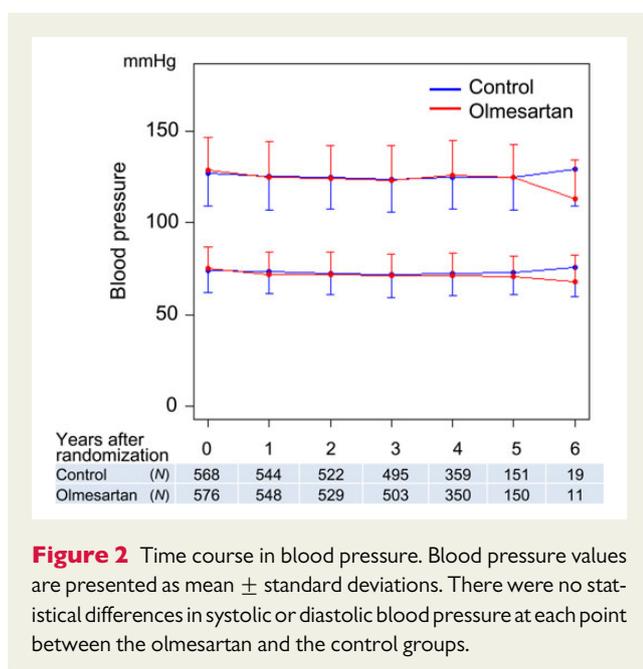
control group. Subgroup analysis revealed that in the olmesartan group treated with ACE inhibitors alone, β-blockers alone, and both of them at the time of randomization, discontinuation of the ARB was noted in 13 (8.0%), 15 (14.2%), and 30 patients (10.0%), respectively, due to the occurrence of the primary endpoint or the end of the study.

Primary endpoint

During a median follow-up of 4.4 years, the primary endpoint occurred in 192 patients (33.2%) in the olmesartan group and in 166 patients (29.2%) in the control group [hazard ratio (HR) 1.18; 95% confidence interval (CI), 0.96−1.46, $P = 0.112$] (*Figure 3* and *Table 3*). Subgroup analysis according to the baseline medication revealed that the incidence of the primary endpoint was more frequent in the olmesartan group than that in the control group, when combined with both ACE inhibitors and β-blockers [38.1% (114/299) vs. 28.2% (88/312), HR 1.47; 95% CI 1.12−1.95, $P = 0.006$], whereas there was no difference in the primary endpoint when combined with β-blockers alone or ACE inhibitors alone (*Figure 4*). Similarly, when combined with both ACE inhibitors and β-blockers, olmesartan was associated with increased incidence of all-cause death [19.4% (58/299) vs. 13.5% (42/312), HR 1.50; 95% CI 1.01−2.23, $P = 0.046$], a component of the primary endpoint, whereas olmesartan was associated with decreased mortality when combined with β-blockers alone [9.4% (10/106) vs. 22.1% (23/104), HR 0.41; 95% CI 0.19−0.85, $P = 0.017$], but not with ACE inhibitors alone (see Supplementary material online, *Figure S1* and *Table S2*). Subgroup analysis revealed that additive use of olmesartan was associated with an increase in the primary endpoint in the subgroups of systolic blood pressure (SBP) of <130 mmHg, estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2, BNP level of >100 pg/mL, and high-sensitive C-reactive protein level of >1 mg/L (see Supplementary material online, *Table S3*), which was primarily due to

the triple combination therapy (see Supplementary material online, *Figure S2*). There were no interactions of the impacts of olmesartan with age, gender, body mass index, diabetes, diastolic blood pressure, left ventricular hypertrophy, LVEF, or use of spironolactone (see Supplementary material online, *Table S3*).
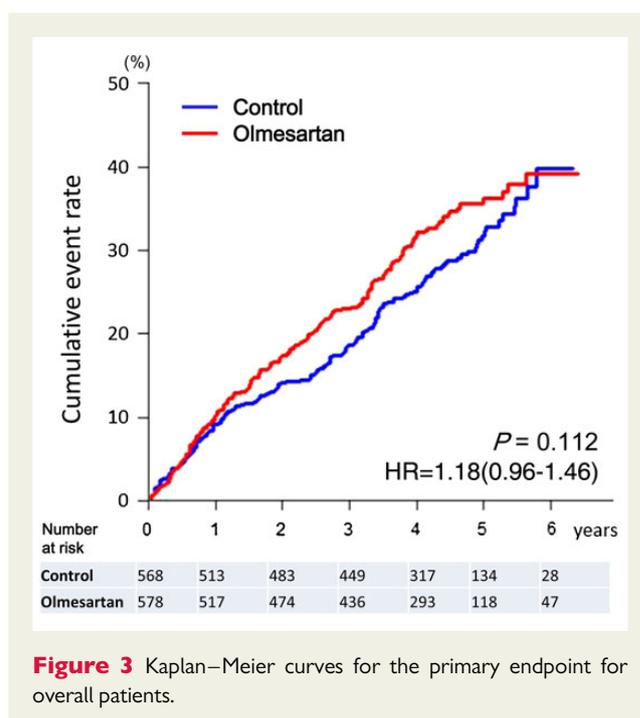
Secondary endpoints

There were no differences in secondary or other endpoints between the olmesartan and the control groups except for development of renal dysfunction [16.8% (97/578) vs. 10.7% (61/568), HR 1.64; 95% CI 1.19−2.26, $P = 0.003$] (*Table 3*). Subgroup analysis revealed that additive use of olmesartan, when combined with both ACE inhibitors and β-blockers, was significantly associated with increased incidence of renal dysfunction [21.1% (63/299) vs. 12.5% (39/312), HR 1.85; 95% CI 1.24−2.76, $P = 0.003$] (see Supplementary material online, *Table S2*). In contrast, when combined with ACE inhibitors alone, use of olmesartan was not associated with renal dysfunction and was rather associated with decreased incidence of atrial fibrillation [2.4% (4/170) vs. 8.8% (13/148), HR 0.26; 95% CI 0.09−0.80, $P = 0.019$] (see Supplementary material online, *Table S2*).

Adverse events

By the end of the study, 16.6% (96/578) of the patients in the olmesartan group discontinued olmesartan due to adverse events and other reasons (see Supplementary material online, *Table S4*). Besides hypotension (7.0%), renal dysfunction (1.2%), and worsening HF (0.7%) were the main adverse events (see Supplementary material online, *Table S4*).

Discussion

In the SUPPORT trial, we examined whether an additive treatment with an ARB, olmesartan, reduces the mortality and morbidity in

Table 3 Incidence of the primary outcome measures, all-cause death, and secondary outcome measures in the overall population

	Control (n = 568) Events, n (%)	Olmesartan (n = 578) Events, n (%)	Hazard ratio	95% CI Lower	Upper	P-value
Primary endpoint	166 (29.2%)	192 (33.2%)	1.18	0.96	1.46	0.112
All-cause death	85 (15.0%)	98 (17.0%)	1.15	0.86	1.54	0.338
Non-fatal acute myocardial infarction	8 (1.4%)	12 (2.1%)	1.479	0.604	3.617	0.391
Non-fatal stroke	26 (4.6%)	34 (5.9%)	1.313	0.788	2.188	0.296
Worsening HF requiring hospitalization	99 (17.4%)	113 (19.6%)	1.148	0.877	1.504	0.316
Secondary endpoints						
Cardiovascular death	38 (6.7%)	48 (8.3%)	1.26	0.82	1.93	0.290
Death due to HF	18 (3.2%)	10 (1.7%)	0.56	0.26	1.20	0.137
Sudden death	8 (1.4%)	18 (3.1%)	2.24	0.97	5.15	0.058
Acute myocardial infarction	12 (2.1%)	13 (2.2%)	1.07	0.49	2.35	0.866
Stroke	26 (4.6%)	34 (5.9%)	1.31	0.79	2.19	0.296
Hospitalization for cardiovascular reasons	179 (31.5%)	199 (34.4%)	1.13	0.92	1.38	0.230
Fatal arrhythmia or appropriate ICD discharge	29 (5.1%)	30 (5.2%)	1.02	0.61	1.69	0.947
New-onset diabetes	60 (10.6%)	70 (12.1%)	1.17	0.83	1.65	0.376
Development of renal dysfunction	61 (10.7%)	97 (16.8%)	1.64	1.19	2.26	0.003
New-onset atrial fibrillation	31 (5.5%)	21 (3.6%)	0.67	0.38	1.16	0.149
Need to modify HF treatments	131 (23.1%)	142 (24.6%)	1.08	0.85	1.37	0.534
Decrease in LVEF	111 (19.5%)	122 (21.1%)	1.11	0.86	1.44	0.419
Increase in BNP levels	198 (34.9%)	217 (37.5%)	1.12	0.92	1.35	0.259

ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide.

Figure 4 Kaplan−Meier curves for the primary endpoint for subgroups according to the baseline medication. (*A*) Patients treated with angiotensin-converting enzyme inhibitors but not with β-blockers. (*B*) Patients treated with β-blockers but not with angiotensin-converting enzyme inhibitors. (*C*) Patients treated with both angiotensin-converting enzyme inhibitors and β-blockers. ACEI, angiotensin-converting enzyme inhibitors; BB, β-blockers.

CHF patients with a history of hypertension and treated with ACE inhibitors and β-blockers. The results revealed that additive use of olmesartan to ACE inhibitors and/or β-blockers did not improve clinical outcomes but worsened renal function in hypertensive CHF patients. Furthermore, subgroup analysis suggested that the triple combination therapy with olmesartan, ACE inhibitors and β-blockers was associated with increased adverse cardiac events and renal dysfunction.

Angiotensin receptor blockers for the management of hypertensive chronic heart failure patients treated with angiotensin-converting enzyme inhibitors and/or β-blockers

Angiotensin receptor blockers have been shown to provide various cardioprotective effects for patients with hypertension and other cardiovascular diseases,[16–19] and are now widely used for the management of CHF worldwide.[20–23] However, there have been no reports to evaluate the additive impact of ARBs in CHF patients with hypertension treated with evidence-based medications. The SUPPORT trial was the first to examine the efficacy of additive use of an ARB to ACE inhibitors and/or β-blockers in hypertensive patients with CHF. The results demonstrated that additive use of olmesartan did not decrease the primary endpoint, a composite of all-cause death, non-fatal acute myocardial infarction, non-fatal stroke, and hospitalization for worsening HF, but increased renal dysfunction in hypertensive CHF patients. Importantly, the triple combination of olmesartan, ACE inhibitors, and β-blockers was associated with an increase in the primary endpoint, particularly in patients with SBP of <130 mmHg, eGFR of <60 mL/min/1.73 m^2, serum BNP levels of ≥100 pg/mL, and high-sensitive CRP level of ≥1.0 mg/L. The triple combination of olmesartan, ACE inhibitors, and β-blockers was also associated with increased incidence of all-cause death and renal dysfunction, whereas the dual combination of olmesartan and ACE inhibitors or β-blockers was not associated with any increase in the primary or secondary endpoints. In addition, it was noteworthy that dual combination of olmesartan and ACE inhibitors was associated with a decrease in new-onset atrial fibrillation and that of olmesartan and β-blockers was associated with decreased mortality without development of renal dysfunction. Thus, it is suggested that the triple combination is harmful but the dual combination therapy, particularly that of olmesartan and β-blockers, could be beneficial in hypertensive patients with CHF. However, dual combination therapy of olmesartan and ACE inhibitors warrants a caution as recent studies suggested that dual blockade of RAS failed to reduce mortality but was associated with an excessive risk of adverse effects, including renal dysfunction, hyperkalaemia, and hypotension, particularly in those without HF.[15–18]

Triple combination of olmesartan, angiotensin-converting enzyme inhibitors, and β-blockers for chronic heart failure

Although it has been shown that combination of ACE inhibitors and ARBs without β-blockers was useful in patients with symptomatic CHF, there has been a controversy for the effectiveness of the dual RAS blockade with ACE inhibitors and ARBs in patients with HFrEF treated with β-blockers.[4–6] In the valsartan heart failure (Val-HeFT) trial,[4] valsartan significantly reduced the combined endpoint of mortality and morbidity in patients with symptomatic CHF; however, the post hoc analysis revealed an increase in adverse effect on mortality and morbidity in the subgroup receiving valsartan, an ACE inhibitor and a β-blocker.[4] In contrast, the CHARM-added trial demonstrated that addition of an ARB candesartan to ACE inhibitors was beneficial in patients with symptomatic CHF regardless of

β-blocker use.[5] Our findings in the SUPPORT trial are consistent with the results of the Val-HeFT study as the triple combination therapy appeared harmful in hypertensive patients with CHF. Although the precise mechanism of the discrepancy for the effectiveness of the triple combination therapy between the Val-HeFT and the CHARM-added studies is unclear, it could be explained by the differences in patient backgrounds; the majority of the patients were in NYHA Class II (62%) in the Val-HeFT study but were in NYHA Class III (73%) in the CHARM-added study. In the present SUPPORT trial, the majority of the patients (93%) were in NYHA Class II. Thus, although the routine use of triple combination of ARBs, ACE inhibitors, and β-blockers should be avoided in hypertensive patients with mildly symptomatic CHF, it remains to be examined whether the triple combination therapy could be beneficial for patients with severe CHF.

Olmesartan for heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction is now recognized as a new entity of HF,[24,25] and represents more than half of HF patients in Japan[19,26,27] and Western countries.[28–30] Although previous RCTs have failed to show the beneficial effects of RAS inhibitors to improve mortality and morbidity in patients with HFpEF,[7–9] a recent report from the Swedish Heart Failure Registry suggested that RAS inhibitors might be beneficial for the disorder.[20] Furthermore, a post hoc analysis of irbesartan in patients with heart failure and preserved ejection fraction study demonstrated that the use of irbesartan was associated with improved outcomes in HFpEF patients with NT-proBNP levels of ≤339 pg/mL.[31] These lines of evidence suggested an benefit of ARBs in patients with HFpEF. In the SUPPORT trial, we enrolled a considerable number of HFpEF patients and examined the clinical impact of olmesartan in a subgroup of patients with preserved EF (≥50%). However, the results remained unchanged even in the subgroups of HFpEF patients.

Relatively low dose olmesartan in the SUPPORT trial

In the ROADMAP trial, olmesartan at a dose of 40 mg once daily was associated with a delayed onset of microalbuminuria in patients with type 2 diabetes, whereas the higher rate of fatal cardiovascular events with olmesartan among patients with pre-existing coronary artery disease was of concern.[32] In the present SUPPORT trial, the mean dose of olmesartan was 9.5 mg/day at the time of randomization and was then increased annually up to 13.3, 15.4, 16.1, 17.4, 17.9, and 16.5 mg/day at 1–6 years, respectively. Since the doses of olmesartan were relatively low compared with the previous studies examining the efficacy of olmesartan,[32,33] there might be a critique that the dose of olmesartan was not enough to achieve its full clinical impacts in the present study. In the Japanese population, however, it was reported that a mean dose of 13.0 mg per day successfully provided adequate reductions in both systolic and diastolic blood pressures along with a significant increase in plasma renin activity as well as a decrease in angiotensin II levels.[34] Thus, it is anticipated that an adequate blockade of angiotensin type I receptor was obtained in the olmesartan group in the SUPPORT trial. Anyway, since the adverse effects of the triple combination of olmesartan, ACE inhibitors, and β-blockers

were noted with this relatively low doses of olmesartan, the present findings should be of clinical importance.

Study limitations

Several limitations should be mentioned for the present study. First, since the SUPPORT trial was conducted in an open-labelled fashion, the interpretation warrants caution. Second, it should be noted that the patients enrolled in the SUPPORT trial had been relatively well-controlled and mildly symptomatic before randomization compared with the previous HF studies; both the mean systolic and diastolic blood pressures (128/74 mmHg) had been already controlled below the target levels recommended by the JNC7[13] and other clinical guidelines,[1,2] and majority of the patients (93%) had been controlled in NYHA Class II. As a result, the patients were characterized by relatively low BNP value (median 80 pg/mL) and modest prescription rate of diuretics (57%). These characteristics were comparable with those in the ALDO-DHF trial that mainly enrolled HFpEF patients in NYHA Class II,[35] but were different from other HFpEF studies that enrolled more symptomatic patients[7–9] and from previous HFrEF studies.[3–5] Furthermore, since the sample size of the present population of patients with HFrEF was small, further studies with a large sample size are needed to examine whether or not the ARB olmesartan is effective for the treatment of those patients. Thus, cautions are warranted when interpreting the present results into other populations including more severely hypertensive or more symptomatic CHF patients. Third, the possible influence of the Great East Japan Earthquake in 2011 in our Tohoku area should be considered, which occurred after the randomization and during the follow-up period of the SUPPORT trial. However, since the results were unaltered even after exclusion of the results from the hospitals located in the area with severe damage, the influence of the disaster may be minimal.

Conclusions

The SUPPORT trial demonstrated that additive use of olmesartan did not improve clinical outcomes but worsened renal function in hypertensive CHF patients treated with evidence-based medications. Particularly, the triple combination therapy with olmesartan, ACE inhibitors, and β-blockers was associated with increased adverse cardiac events.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Appendix

The SUPPORT trial investigators

Executive committee

H. Shimokawa (principal investigator), M. Fukuchi, T. Goto, T. Hiramoto, K. Inoue, A. Kato, T. Komaru, M. Ohe, N. Sekiguchi, N. Shiba, T. Shinozaki, M. Sugi, K. Tamaki.

Steering committee

T. Hiramoto, K. Inoue, A. Kato, M. Ogata, S. Sato, M. Sugi.

Endpoint evaluation committee

N. Ishide, S. Ibayashi, Y. Maruyama.

Ethics committee

I. Ohno, K. Tamaki.

Data safety monitoring board

H. Ogawa, M. Kitakaze.

Statistical analysis board

I. Tsuji, T. Watanabe, K. Sugiyama.

Collaborating hospitals and active investigators by prefecture

Aomori prefecture

S. Oyama (Towada City Hospital).

Iwate prefecture

E. Nozaki, A. Nakamura, T. Takahashi, H. Endo, S. Fukui, S. Nakajima (Iwate Prefectural Central Hospital). M. Nakagawa, T. Nozaki, T. Yagi (Iwate Prefectural Isawa Hospital).

Akita prefecture

S. Horiguchi, E. Fushimi, Y. Sugai, S. Takeda, K. Fukahori, K. Aizawa (Hiraka General Hospital).

Yamagata prefecture

M. Ohe, T. Tashima, K. Sakurai, T. Kobayashi (Kojirakawa Shiseido Hospital). T. Goto, M. Matsui, Y. Tamada, T. Yahagi, A. Fukui, K. Takahashi, K. Takahashi, Y. Kikuchi (Yamagata Prefectural Central Hospital).

Miyagi prefecture

K. Akai (Ishinomaki City Hospital). H. Kanno, J. Kaneko (Katta General Hospital). S. Suzuki, K. Takahashi (KKR Tohoku Kosai Hospital). K. Akai (Kurihara Central Hospital). D. Katayose (Miyagi Rifu Ekisaikai Hospital). S. Onodera, T. Hiramoto, S. Komatsu, M. Chida, K. Iwabuchi, M. Takeuchi, H. Yahagi, N. Takahashi (Osaki Citizen Hospital). K. Otsuka, Y. Koseki, M. Morita (Saito Hospital). T. Shinozaki, T. Ishizuka, N. Onoue, N. Yamaguchi, H. Fujita (Sendai Medical Center). A. Katoh, S. Namiuchi, T. Sugie, K. Saji, T. Takii, (Sendai Open Hospital). A. Sugimura, J. Ohashi (Sendai Red Cross Hospital). M. Fukuchi, M. Ogata, T. Tanikawa, O. Kitamukai (Sendai Tokushukai Hospital). Y. Matsumoto (Shizugawa Public Hospital). K. Inoue, J. Koyama, T. Tomioka, H. Shioiri, Y. Ito (South Miyagi Medical Center). H. Kato, C. Takahashi, A. Kawana (Tohoku Rosai Hospital). Y. Sakata, K. Ito, M. Nakayama, K. Fukuda, J. Takahashi, S. Miyata, K. Sugimura, K. Sato, Y. Matsumoto, M. Nakano, T. Shiroto, R. Tsuburaya, K. Nochioka, H. Yamamoto, T. Aoki, K. Hao, M. Miura, M. Kondo, S. Tatebe, S. Yamamoto, H. Suzuki, K. Nishimiya, N. Yaoita (Tohoku University Hospital).

Fukushima prefecture

M. Sugi, Y. Yamamoto, S. Toda, Y. Minatoya, Y. Takagi, Y. Hasebe, T. Nihei, K. Hanawa (Iwaki Kyouritsu Hospital). K. Fukuda (Watanabe Hospital).

Head office and coordinating center

Y. Sakata, J. Takahashi, S. Miyata, K. Nochioka, M. Miura, S. Tadaki, R. Ushigome, T. Yamauchi, K. Sato, K. Tsuji, T. Onose, R. Abe, C. Saga, J. Suenaga, Y. Yamada, J. Kimura, H. Ogino, I. Oikawa, S. Watanabe, M. Saga, M. Washio, K. Nagasawa, S. Nagasawa, S. Kotaka, W. Komatsu, R. Hashimoto, Y. Ikeno, T. Suzuki, H. Hamada (Tohoku University Hospital)

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