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

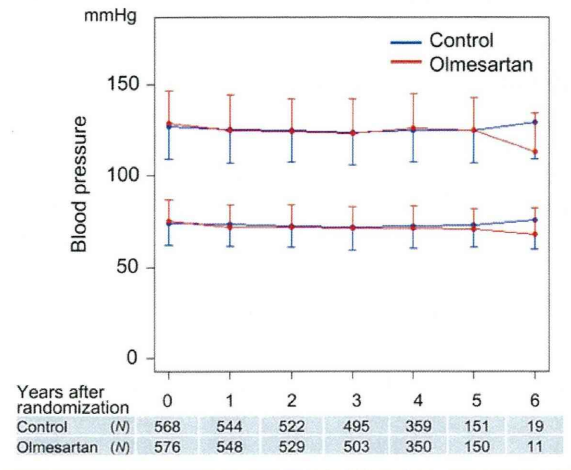

Figure 2 Time course in blood pressure. Blood pressure values are presented as mean ± standard deviations. There were no statistical differences in systolic or diastolic blood pressure at each point between the olmesartan and the control groups.

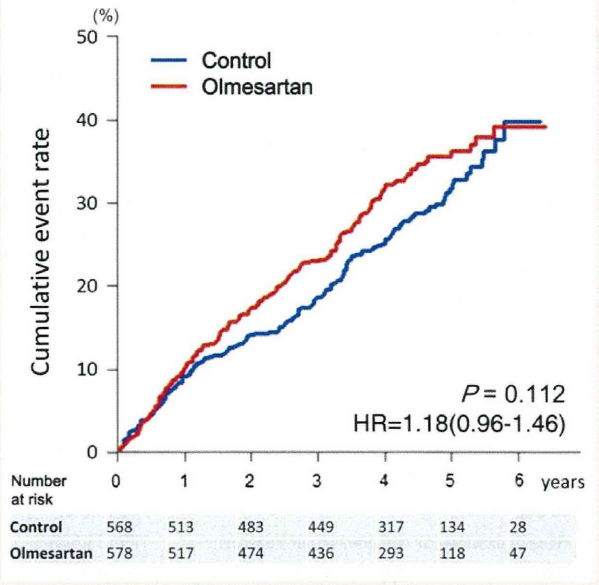

Figure 3 Kaplan–Meier curves for the primary endpoint for overall patients.

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)	Olmesartan (n = 578)	Hazard ratio	95% CI		P-value
	Events, n (%)	Events, n (%)		Lower	Upper	
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.

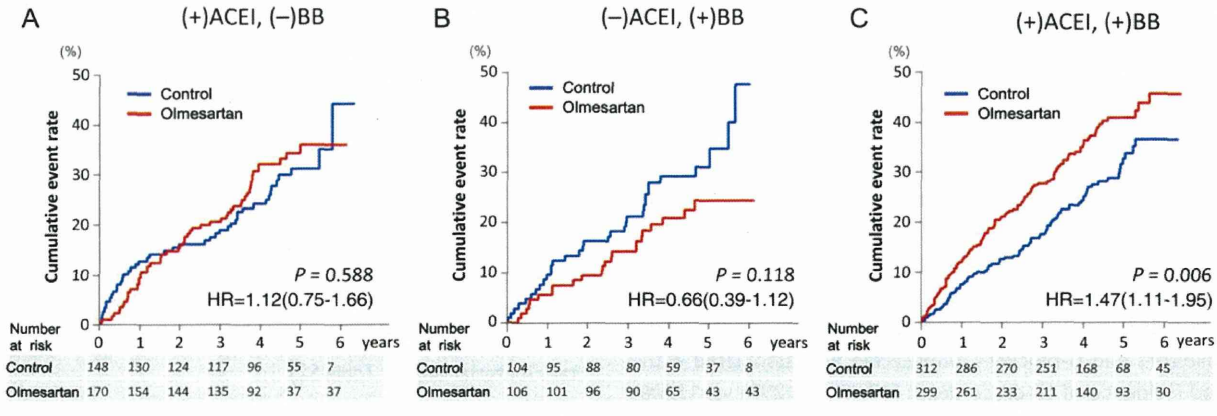

Figure 4 Kaplan–Meier curves for the primary endpoint for subgroups according to the baseline medication. (*A*) Patients treated with angiotensin-converting enzyme inhibitors but not with β-blockers. (*B*) Patients treated with β-blockers but not with angiotensin-converting enzyme inhibitors. (*C*) Patients 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 $\geq$100 pg/mL, and high-sensitive CRP level of $\geq$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 $\leq$339 pg/mL.[31] These lines of evidence suggested an benefit of ARBs in patients with HFpEF. In the SUPPORT trial, we enrolled a considerable number of HFpEF patients and examined the clinical impact of olmesartan in a subgroup of patients with preserved EF ($\geq$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.

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ORIGINAL ARTICLE
Heart Failure

Prognostic Impact of Subclinical Microalbuminuria in Patients With Chronic Heart Failure

– Report From the CHART-2 Study –

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Background: Microalbuminuria, traditionally defined as urinary albumin/creatinine ratio (UACR) ≥30 mg/g, is a risk factor for mortality even in patients with preserved glomerular filtration rate (GFR). The prognostic impact of subclinical microalbuminuria, however, remains unknown in patients with chronic heart failure (CHF).

Methods and Results: In the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 Study, we enrolled 2,039 consecutive symptomatic CHF patients (median age, 67.4 years; 68.9% male) after excluding those on hemodialysis. On classification and regression tree analysis, UACR=10.2 mg/g and 27.4 mg/g were identified as the first and second discriminating points to stratify the risk for composite of death, acute myocardial infarction, HF admission and stroke, therefore subclinical microalbuminuria was defined as UACR ≥10.2 and <27.4 mg/g. There were 506 composite endpoints (24.8%) during the median follow-up of 2.69 years. On Kaplan-Meier analysis and multivariate Cox modeling, subclinical microalbuminuria was significantly associated with increased composite endpoints with hazard ratios of 1.90 (P<0.001) and 2.29 (P<0.001) in patients with preserved (>60 ml·min^{-1}·1.73 m^{-2}, n=1,129) or mildly reduced eGFR (30–59.9 ml·min^{-1}·1.73 m^{-2}, n=789), respectively. In patients with severely reduced GFR (eGFR <30 ml·min^{-1}·1.73 m^{-2}, n=121), >80% had microalbuminuria or macroalbuminuria, and only 9.1% were free from any composite endpoints.

Conclusions: Subclinical microalbuminuria was associated with increased risk of cardiovascular events in CHF patients with mildly reduced or preserved renal function. (*Circ J* 2014; **78:** 2890–2898)

Key Words: Chronic heart failure; Chronic kidney disease; Prognosis; Subclinical microalbuminuria

Microalbuminuria, traditionally defined as between 30 and 300 mg/g urinary albumin/creatinine ratio (UACR),[1] is an independent risk for mortality in the general population and in patients with hypertension or diabetes mellitus.[2–4] The latest classification of chronic kidney disease (CKD) has defined microalbuminuria as a risk for adverse outcome even in patients with preserved glomerular filtration rate (GFR; ml·min^{-1}·1.73 m^{-2}).[1] Recently, however, several large population studies suggested that the normal albuminuria level is much lower than 30 mg/g.[5–7] For example, the Prevention of Renal and Vascular End/stage Disease (PREVEND) Trial in the Netherlands reported that the median UACR was 6.1 mg/g (95% confidence interval [95% CI]: 2.3–28.7 mg/g),[5] and the most recent evaluation of the National Health and Nutrition Examination Survey (NHANES) Data noted a mean UACR of 12.3 mg/g in young healthy participants.[6] Moreover, subclinical microalbuminuria was significantly associated with the development of heart failure (HF) in the general population.[8,9] Thus, it is now considered that even subclinical microalbuminuria, usually <30 mg/g UACR, is likely to have a prognostic impact.[8–14]

Editorial p2838

In patients with chronic heart failure (CHF), it has been reported that microalbuminuria is also associated with poorer

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Table 1. Baseline Patient Characteristics

UACR (mg/g)	All patients (n=2,039)	Normoalbuminuria <10.2 (n=614)	Subclinical microalbuminuria 10.2–27.3 (n=534)	Microalbuminuria 27.4–300 (n=684)	Macroalbuminuria >300 (n=207)	P-value
Age (years)	67.5±12.4	64.5±12.5	67.7±12.1	69.7±11.8	68.5±12.5	<0.001
Male (%)	68.9	74.3	65.9	65.6	71.0	0.003
History of admission for HF (%)	53.6	52.4	50.4	55.3	59.4	0.21
Ischemic heart disease (%)	46.2	44.3	49.1	42.5	56.5	0.002
Comorbidity (%)						
Hypertension	82.5	76.1	82.0	86.4	89.9	<0.001
Diabetes	40.3	31.3	34.6	45.2	66.0	<0.001
Hyperlipidemia	76.0	76.9	76.4	73.4	81.2	0.12
Hyperuricemia	46.8	44.8	42.7	46.6	63.8	<0.001
Atrial fibrillation	32.2	28.3	31.4	37.6	28.4	<0.001
Cerebrovascular disease	16.7	12.1	16.7	19.9	19.8	0.001
Clinical status						
NYHA class 3 and 4 (%)	11.2	9.0	10.8	12.4	15.0	0.03
BMI (kg/m^2)	23.7±4.6	23.8±4.2	23.6±4.4	23.7±4.8	23.5±5.2	0.81
SBP (mmHg)	127.0±18.7	123.2±16.7	126.0±17.4	128.8±19.5	134.3±21.7	<0.001
DBP (mmHg)	72.7±12.0	72.1±11.5	72.8±11.2	73.3±12.6	73.8±15.0	0.40
Heart rate (beats/min)	72.3±14.9	70.6±14.2	72.3±14.7	73.5±15.5	73.8±15.0	0.002
Laboratory data						
LVEF (%)	55.3±15.7	54.1±16.2	55.8±15.7	55.7±15.6	55.7±14.8	0.20
LVEF ≥50% (%)	64.6	62.8	63.3	66.7	66.5	0.41
LVDd (mm)	52.5±9.4	53.4±9.9	52.4±9.3	52.1±9.4	52.0±8.6	0.08
Hemoglobin (g/dl)	13.3±2.2	13.7±2.1	13.4±2.2	13.2±2.1	12.3±2.6	<0.001
BUN (mg/dl)	19.3±10.4	17.0±6.2	17.7±6.5	20.2±11.8	26.7±17.4	<0.001
Serum sodium (mEq/L)	141.0±2.8	141.2±2.5	140.8±2.7	140.8±3.0	141.1±3.2	0.02
Serum potassium (mEq/L)	4.4±0.4	4.4±0.4	4.3±0.4	4.3±0.4	4.4±0.5	0.02
GFR (ml·min^{-1}·1.73m^{-2})	62.8±20.9	66.9±18.4	66.1±19.1	60.8±21.5	48.7±23.0	<0.001
UACR (mg/g)	21.5 (8.3–74.4)	5.8 (3.9–7.5)	16.5 (13.0–21.4)	64.0 (39.6–121)	679.0 (407–1,283)	<0.001
BNP (pg/ml)	99.3 (39.0–229)	67.8 (27.2–148)	96.0 (37.9–213)	130.5 (54.2–264)	180.1 (64.4–373)	<0.001
Medication (%)						
RAS inhibitor	73.2	70.4	71.3	74.9	80.7	0.02
β-blocker	52.2	52.5	51.5	52.7	53.6	0.90
CCB	37.3	27.5	33.9	43.6	54.6	<0.001
Loop diuretic	44.6	43.3	42.9	44.4	53.6	0.049
Aldosterone antagonists	25.9	29.2	24.7	26.6	17.4	0.008
Statins	40.5	39.1	41.6	37.9	50.7	0.008
Outcome						
Composite endpoints	24.8	13.4	23.4	31.6	40.1	<0.001

Data given as mean±SD, %, or median (IQR). BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CCB, calcium channel blocker; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HF, heart failure; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RAS, renin-angiotensin system; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio.

prognosis regardless of the presence of diabetes, hypertension or renal dysfunction.[15–17] Indeed, we recently found that urinary albumin excretion has a significant prognostic impact in CHF patients with preserved ejection fraction.[17] In contrast, only a few studies previously examined the clinical impact of subclinical microalbuminuria in CHF patients, and furthermore they did not examine that of subclinical albuminuria in detail.[18,19] Thus, it remains to be clarified whether subclinical microalbuminuria also has a significant prognostic impact in CHF patients, particularly with a reference to renal function. Thus, in the present study, we examined microalbuminuria level to determine mortality or cardiovascular events in CHF patients according to renal function status, in the Chronic Heart failure Analysis and Registry in the Tohoku district 2 (CHART-2) Study.[17,20–23]

Methods

Subjects and Inclusion Criteria

Details of the design, purpose and basic characteristics of the CHART-2 Study have been described previously (NCT00418041).[17,21–23] Briefly, the CHART-2 Study was started in October 2006 and the entry period was successfully closed in March 2010 with 10,219 patients in stages B/C/D HF according to the ACCF/AHA guideline.[24] The study protocol was approved by the local ethics committee in the 24 participating hospitals and written informed consent was obtained from all

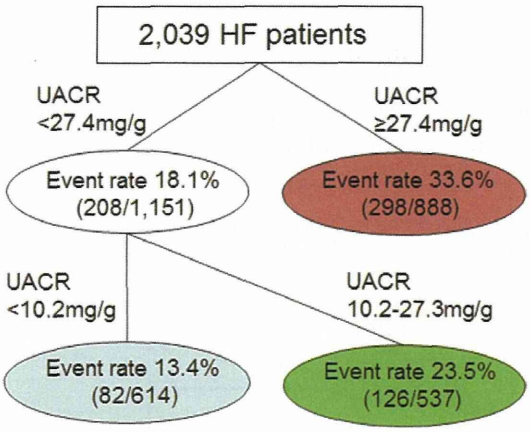

Figure 1. Classification and regression tree (CART) analysis for urinary albumin/creatinine ratio (UACR). CART identified the first discriminating point of UACR 27.4 mg/g, and the second discriminating point of UACR 10.2 mg/g. HF, heart failure.

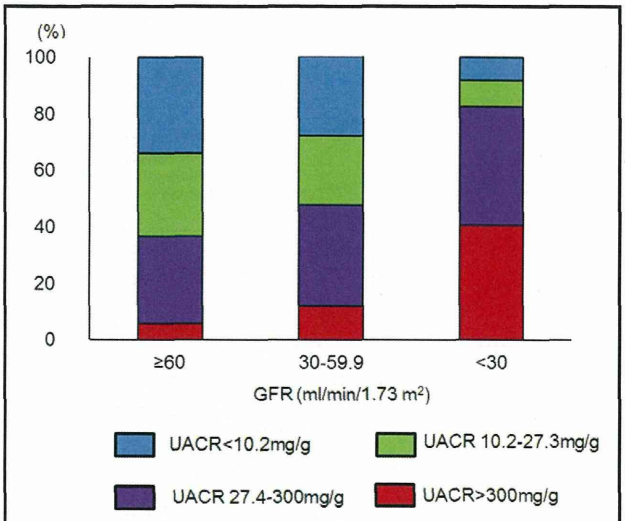

Figure 2. Distribution of urinary albumin/creatinine ratio (UACR) according to estimated glomerular filtration rate (eGFR). More than 80% of the patients with eGFR <30 ml·min^{-1}·1.73 m^{-2} had clinical albuminuria.

patients. Patients were classified as having HF by experienced cardiologists using the criteria of the Framingham Heart Study.[25] All data and events will be surveyed at least once a year until March 2018.[17,21–23]

Among the 10,219 patients, we enrolled 4,735 consecutive patients with stage C/D CHF in the present study. We excluded 63 patients on hemodialysis, 2,591 without UACR measurement, and 42 without appropriate follow-up. Finally, 2,039 patients with stage C/D CHF were included in the present study.

UACR and GFR Measurement

Albuminuria was quantitatively evaluated using UACR. Urine samples were collected in outpatient clinics or before discharge, and urine albumin was measured in a central laboratory (SRL, Tokyo, Japan) to calculate UACR. Estimated GFR (eGFR; ml·min^{-1}·1.73 m^{-2}) was calculated using the modified Modification of Diet in Renal Disease equation with the Japanese coefficient[26] at the time of enrollment. We defined preserved eGFR as ≥60 ml·min^{-1}·1.73 m^{-2}, mildly reduced eGFR as 30–59.9 ml·min^{-1}·1.73 m^{-2}, and severely reduced eGFR as <30 ml·min^{-1}·1.73 m^{-2} according to the guidelines.[1]

Study Outcomes

The outcomes of the present study included composite of death, acute myocardial infarction, HF admission and stroke. Mode of death was determined by the attending physician and was confirmed by 1 independent physician who was a member of the Tohoku Heart Failure Association.[20]

Statistical Analysis

Classification and regression tree (CART) analysis[27] was done in order to identify the cut-off points of UACR to classify CHF patients for the composite endpoints. CART analysis is an empirical and statistical technique based on recursive partitioning of the data space to predict response.[28] The models are obtained by binary discrimination of the data by predictors, and the discrimination variable and discriminating point are automatically selected from possible predictor values to achieve the best fit. Then, one or both "child nodes" are discriminated into 2 or more regions recursively, and the process continues until some stopping rule is applied.[28] Finally, the result of this process is represented as a binary decision tree. We divided the patients into 4 groups according to UACR cut-offs obtained 1 CART analysis as follows: normoalbuminuria, subclinical microalbuminuria, microalbuminuria, and macroalbuminuria.

Kaplan-Meier curves and Cox proportional hazard models were used to compare the risk for composite endpoints among the 4 groups. Cox proportional hazard models were adjusted for the following covariates that could potentially influence outcome: age, sex, New York Heart Association (NYHA) class, history of HF admission and malignant tumor, ischemic etiology of HF, systolic blood pressure, heart rate, left ventricular ejection fraction (LVEF), body mass index, hemoglobin, serum sodium, serum potassium, blood urea nitrogen (BUN), brain natriuretic peptide (BNP), eGFR, comorbidities (atrial fibrillation, diabetes mellitus, hyperlipidemia, hyperuricemia and cerebrovascular disease), and medications (β-blockers, renin-angiotensin system [RAS] inhibitors, loop diuretics, aldosterone antagonists, calcium channel blockers and statins). We also performed subgroup analyses based on sex, age (<median or ≥median), LVEF (<50% or ≥50%), history of hypertension and diabetes mellitus, and medications (β-blockers, RAS inhibitors and statins). In addition, CART analysis was done using both UACR and eGFR to evaluate the importance of subclinical microalbuminuria on renal function. Comparisons among the 4 groups were done using chi-squared test. Continuous data are described as mean±SD and discrete data as %. UACR and BNP are described as median.

SPSS Statistics 21.0 (SPSS, Chicago, IL, USA) and R 2.15.2 were used for statistical analysis.[27] The statistical significance was defined as 2-sided $P<0.05$. Comparison of the baseline characteristics among the 4 groups was performed using ANOVA for continuous variables and chi-squared test for categorical variables. Comparison of BNP and UACR among the 4 groups was done using Kruskal-Wallis test.

Results

Baseline Characteristics

Table 1 lists patient baseline characteristics. Median age was