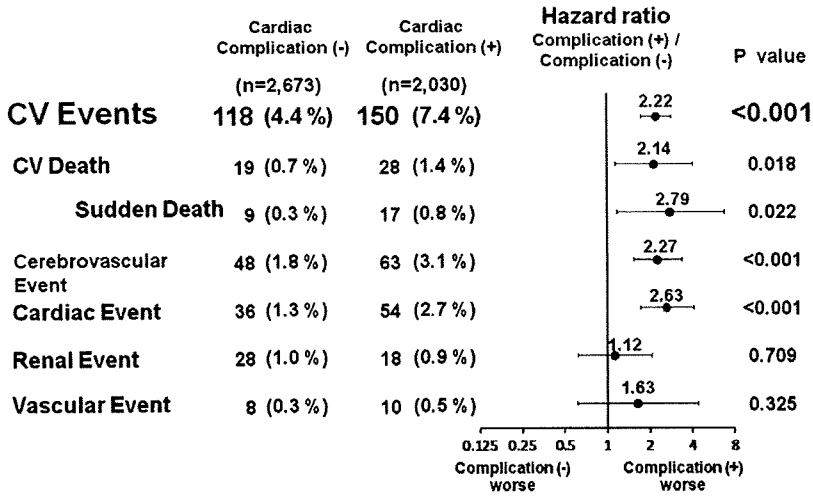

Figure 3. Comparison of each primary endpoint category in patients with or without cardiac complications. CV events, cardiovascular events; CV death, cardiovascular death.

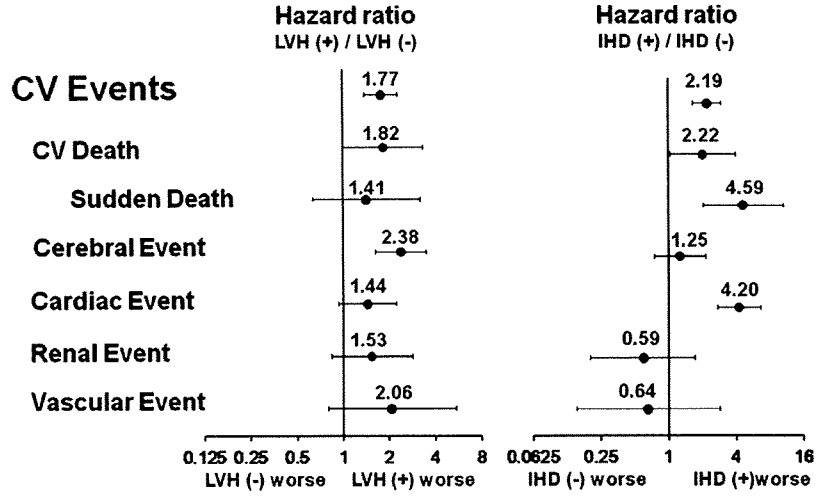

Figure 4. Comparison of each primary endpoint category in patients with or without left ventricular hypertrophy and in patients with or without ischemic heart disease. LVH, left ventricular hypertrophy; IHD, ischemic heart disease; CV events, cardiovascular events; CV death, cardiovascular death.

each event category of CV events between LVH and IHD. As shown in **Figure 4**, LVH was strongly associated with the onset of cerebrovascular events (adjusted HR: 2.38; 95%CI: 1.62–3.48; P<0.001 in LVH, and adjusted HR: 1.25; 95%CI: 0.74–2.12; P=0.401 in IHD), whereas IHD was strongly associated with the onset of CV death (adjusted HR: 1.82; 95%CI: 0.99–3.28; P=0.053 in LVH, and adjusted HR: 2.22; 95%CI: 1.02–3.96; P=0.043 in IHD), especially sudden death (adjusted HR: 1.41; 95%CI: 0.63–3.17; P= 0.408 in LVH, and adjusted HR: 4.59; 95%CI: 2.02–10.41; P<0.001 in IHD), and other cardiac events (adjusted HR: 1.44; 95%CI: 0.93–2.21; P=0.100 in LVH, and adjusted HR: 4.20; 95%CI: 2.69–6.55; P<0.001 in IHD). Neither LVH nor IHD was related to the onset of renal or vascular events.

Discussion

The present study extends the clinical implication of cardiac complications such as LVH and IHD in high-risk hypertensive patients. Because the baseline clinical characteristics were different in patients with or without cardiac complications, the HRs for CV events were adjusted by the baseline characteristics. We demonstrated that cardiac complications are an independent predictor for CV events. Moreover, LVH and IHD were independent predictors for CV events. To our knowledge, this is the first report of the separate effect of LVH and IHD on the incidence of CV events, including renal events, analyzed in high-risk hypertensive patients. Although BP lowering was substantial in both groups of patients, the achieved BP was slightly different between them. Because the BP level achieved in patients with cardiac complications was lower than that in the patients without cardiac complications, this result was not caused by inadequacy of BP lowering in patients with cardiac complications.

LVH is an adaptive response that reduces LV wall stress against volume and pressure overload[10,11] Although this was originally thought to be a compensatory and beneficial response to normal wall stress, large population studies have provided evidence that LVH confers increased risk for CV events[12–15] The reasons why LVH is a powerful predictor for CV events are not yet clear, and there are various mechanisms to explain the relationship between LVH and CV events[16,17] Two important concepts have been proposed for the clinical implication of LVH. First, LVH has been predominantly considered a valuable surrogate index for CV events, reflecting longstanding exposure to high BP. There-

fore, the complication of LVH indicates advanced arteriolosclerosis in various organs including the brain and kidneys![18–20] The present study results indicated a strong relationship between LVH and the onset of cerebrovascular events. Elevated SBP, which sets up LVH, is associated with a profound increase in the risk of cerebrovascular events. The ARIC study demonstrated that incident stroke was predicted by the echocardiographic LV mass index (LVMI)?[21] Another study also revealed that LVH was associated closely with stroke, and that the risk ratio of the LVMI was 1.020 for each 1 g/m^2 increase?[22] Second, LVH may contribute directly to CV events through pathological changes, including fibrosis and relative ischemia caused by hypertrophy![17,23] LVH is related to adverse LV remodeling as a result. We believed that the reason why LVH failed to predict the onset of CV events other than cerebrovascular events is mainly for statistical reasons based on the small numbers in this study. The total number of cerebrovascular events was 111, whereas cardiac events occurred in only 90 cases.

This study indicated that a history of prior IHD is closely connected with CV events. In particular, the adjusted HRs of sudden death and cardiac events, including MI, AP and congestive HF, in patients with IHD was almost 3-fold or more than those in patients with LVH. Because these events are closely related to coronary lesions, the effect of a history of IHD was strong. Conversely, hypertension increases the risk of CV events including stroke, HF and death after MI?[24] Ravipati et al reported that the risk ratio of prior MI was 3.29 for either new stroke or new MI or death in 306 patients with hypertension or diabetes mellitus?[22]

Study Limitations

First, because this analysis was post-hoc, the numbers in each category of CV events, particularly renal and vascular events, may not be enough to analyze the effect of cardiac complications on these events. Recently, higher urinary albumin excretion has been observed in patients with LVH?[25–27] suggesting that cardiac and glomerular vascular damage may occur in parallel. Systemic inflammation and endothelial damage are possible mechanisms of the relationship between them?[28] In the present study, however, cardiac complications, both LVH and IHD, failed to predict the onset of renal events. Therefore, we should focus on the time-course of renal function as well as the onset of renal events. Accordingly, the effects of cardiac complications on the kidney remain unknown. Second, in this study, hypertensive patients with any one of the high-risk factors, including LVH and IHD, were enrolled, so when we evaluated the data of patients with or without cardiac complications, the analyses had to be adjusted by the baseline characteristics because of their statistical differences. Third, the definition of LVH consisted of ECG criteria (SV1+RV5 ≥3.5 mV) and echocardiographic criteria (LV wall thickness ≥12 mm). Because echocardiography is only performed when feasible, there were small numbers of patients who underwent echocardiography. Accordingly, we had to combine different criteria of either ECG or echocardiography. Fourth, 3.2 years of mean follow-up may not be long enough to evaluate the relationship between underlying risks and the incidence of CV events. The CASE-J trial was extended for 3 years from 2006 as an observational study named CASE-J Ex?[29] and it may resolve this issue in the near future.

In conclusion, cardiac complications are independent predictors for CV events in Japanese high-risk hypertensive patients, but the clinical implication differs between LVH and IHD. LVH is related to cerebrovascular events and IHD is related to cardiac death, including sudden death and other cardiac events.

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Disclosures

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Improvement of Quality of Life With Nocturnal Oxygen Therapy in Heart Failure Patients With Central Sleep Apnea

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Background: Previously, we reported the benefit of 12 weeks of home oxygen therapy (HOT) in patients with central sleep apnea (CSA) and heart failure (HF). In the present study, we attempted to confirm the sustained efficacy of HOT in the long term treatment.

Methods and Results: In the present study, 51 patients with CSA and HF (New York Heart Association (NYHA) functional classes II–III) were assigned to receive either nocturnal oxygen (HOT group n=26) or usual breathing (control group n=25) for 52 weeks. In the HOT group, greater reduction in apnea and hypopnea and greater increase in nocturnal oxygen saturation were observed. These changes were associated with greater improvement in the Specific Activity Scale (0.82±1.17 vs −0.11±0.73 Mets, P=0.009) in NYHA functional class (P=0.007) and in ejection fraction (5.45±11.94 vs 1.28±9.77%). There were no significant differences in the cardiac event rates; however, the later divergence favored the HOT group.

Conclusions: The 52-week HOT was well tolerated and the benefit observed in the 12-week trial was sustained over a prolonged period of time. HOT was considered to be a valuable non-pharmacological therapeutic addition for HF patients with CSA. (*Circ J* 2009; **73:** 1255–1262)

Key Words: Heart failure; Oxygen; Prognosis; Quality of life; Sleep apnea

With the aging of society, heart failure (HF) is becoming increasing prevalence[1] constituting a major cause of death in elderly patients[2] A number of innovative pharmacological therapy developed for HF are palliative rather than curative, and morbidity and mortality rates still remaining high. Therefore, intensive interest and passion have been centered on determining all treatable conditions that can exacerbate HF.

There is now convincing evidence that obstructive sleep apnea (OSA) and central sleep apnea (CSA), collectively referred to as sleep disordered breathing (SDB), are closely linked to HF, and these comorbid associations appear to have adverse prognostic implications[3–5] Although CSA is relatively rare in the general population, prospective studies have revealed that 33–82% of patients with chronic HF (CHF) have evidence of CSA and characteristic Cheyne-Stokes respiration (CSR), even in the absence of profound oxygen desaturation[6–12] The effects of nocturnal nasal oxygen on CSA were first described in 1908 by Pembrey. He investigated the effect of breathing pure oxygen in 3 cases and found that apnea, after a delay of 2–3 min, was abolished[13] After 100 years, studies on the effects of oxygen on SDB in patients with CHF are still limited. In most of the reports, only small groups of patients have been enrolled and the results are divergent and inconclusive[14–18] Previously, we reported that a 12-week treatment with nocturnal oxygen significantly improved New York Heart Association (NYHA) functional class, and Specific Activity Scale scores as a measure of quality of life (QOL), along with an improvement of SDB in CHF patients with CSR-CSA[19] Left ventricular ejection fraction (LVEF) also increased from baseline to the end of the study. In the present study, we assessed the effects of prolonged use of home oxygen therapy (HOT) to confirm that the benefit observed in the previous short-term study is sustained with longer-term therapy.

Methods

Study Population

Ambulatory patients aged over 20 years with clinical evidence of CHF were enrolled from 19 centers if they met the following criteria: (1) symptomatic but stable HF (NYHA functional class II or III) with a history of hospitalization within 1 year, (2) LVEF within 6 months of the diagnostic sleep study ≤45%, (3) 4% oxygen desaturation

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Members of the CHF-HOT Study Group are listed in Appendix 1.

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Table 1. Baseline Characteristics of the Patients

	HOT	Control	P value
No. of patients	26	25	
Age (years)	67.2±9.6	68.5±12.4	0.688
M/F	21/5	21/4	0.762
Body weight (kg)	62.38±10.40	60.93±9.49	0.614
Systolic blood pressure (mmHg)	120.3±18.9	115.7±18.5	0.388
Diastolic blood pressure (mmHg)	71.0±10.3	68.1±9.5	0.306
Underlying heart disease			
DCM/IHD/HHD/VHD/Others (n)	9/11/1/4/1	11/11/2/0/1	0.341
Duration of CHF (years)	5.17±7.11	4.54±4.17	0.658
Concomitant medication			
Digi/Diur/ACEI/β-blockers (n)	7/24/23/18	5/25/19/18	–*
Specific Activity Scale (Mets)	3.81±1.23	3.98±1.12	0.603
NYHA functional class II/III (n)	16/10	20/5	0.152
LVEF (%)	31.89±8.74	31.74±7.28	0.946
CTR (%)	58.75±7.39	55.69±4.83	0.088
ODI (dip/h)	20.86±9.20	21.92±10.70	0.704
AHI (events/h)	20.01±11.24	21.96±11.68	0.546
BNP (pg/ml)	516.3±434.8	413.1±428.2	0.397
ANP (pg/ml)	156.4±126.2	126.0±98.4	0.344
NE (pg/ml)	597.6±393.7	617.2±270.1	0.837
$PaCO_2$ (mmHg)	37.34±3.90	37.45±4.71	0.931

P values were calculated by the chi-square test, t-test or Wilcoxon test. Mean±SD.
*There was no difference between groups in the prescription rate of each drug.
HOT, home oxygen therapy; DCM, dilated cardiomyopathy; IHD, ischemic heart disease; HHD, hypertensive heart disease; VHD, valvular heart disease; Digi, digitalis; Diur, diuretics; ACEI, angiotensin-converting enzyme inhibitor (including angiotensin-receptor blocker); NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CTR, cardiothoracic ratio; ODI, oxygen desaturation index; AHI, apnea-hypopnea index; BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide; NE, norepinephrine; $PaCO_2$, arterial partial pressure of carbon dioxide.

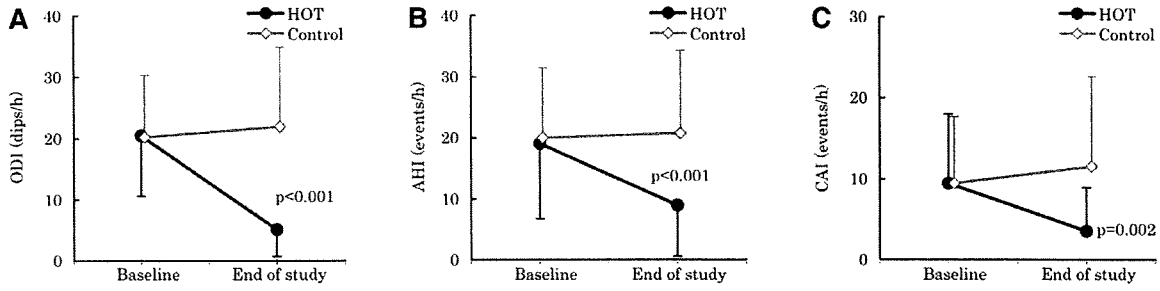


Figure 1. Effects of 52-week nocturnal home oxygen therapy (HOT) on the oxygen desaturation index (ODI) (**A**), apnea/hypopnea index (AHI) (**B**) and central sleep apnea index (CAI) (**C**). Oxygen saturation improved and AHI and CAI were reduced in the HOT group, whereas these parameters remained unchanged in the control group. Mean±SD.

index (ODI) of ≥5 dips/h, (4) at least 5 episodes of apnea and hypopnea per hour of sleep, of which more than 50% were central in nature at screening test.[20] Exclusion criteria were: predominant OSA, pregnancy, unstable angina, myocardial infarction within the previous 3 months, and significant renal, neurological or respiratory disease. The study protocol was approved by the institutional ethics review board and written informed consent was given by all patients prior to entry.

Study Design, Intervention and Procedures

Each patient underwent routine clinical assessment, including radiologic, electrocardiographic and echocardiographic studies, and measurement of plasma neuropeptides. Physical activity was determined from the Specific Activity Scale questionnaire.[21] Polysomnography (PSG) or polygraphic recordings of cardiorespiratory parameters and percutaneous arterial oxygen saturation (SpO_2) was performed. The investigators sent a fax the coordinating center when they enrolled a new patient and randomization was performed according to the method of minimization by 6 factors (laboratory, age, sex, Specific Activity Scale, ODI and LVEF); each patient was assigned to receive oxygen at a rate of 3 L/min through a nasal cannula[19] (HOT group) or to allow usual breathing for 52 weeks (control group). Oxygen was delivered via a 92% concentrator (TO-90–3N, Teijin Pharma Ltd, Tokyo, Japan). The patients assigned to the HOT group were instructed to use nasal oxygen for at least 4 h/night. Compliance was monitored by the patients' reports and the inbuilt concentrator tachometer (TOMS®, Teijin Pharma Ltd). Outpatient visits were scheduled every 4 weeks during which physical findings, NYHA functional class, the Specific Activity Scale questionnaire, and adverse events were assessed. At weeks of 12, 24 and 52, evaluation included electrocardiography, echocardiography, chest X-ray, plasma neuropeptides, sleep study, and arterial blood gas analysis. Measurements of plasma neuropeptides were also repeated at weeks 4 and 36.

The patients were followed up to for 52 weeks or until the primary endpoints occurred. The outcome was assessed

Table 2. Changes in Variables for Efficacy in the HOT and Control Groups

	Group	Baseline	End of study	Difference	P value
SDB indicators during sleep					
AHI (events/h)	HOT	21 (19.05±12.29)	21 (8.98±8.43**)	21 (−10.07±10.49)	<0.001
	Control	21 (20.00±11.45)	21 (20.75±13.51)	21 (0.75±11.25)	
CAI (events/h)	HOT	21 (9.44±8.59)	21 (3.54±5.40**)	21 (−5.9±7.63)	0.002
	Control	21 (9.48±8.23)	21 (11.27±11.15)	21 (1.8±9.38)	
OAI (events/h)	HOT	21 (2.23±3.35)	21 (4.35±4.26*)	21 (2.12±4.51)	0.093
	Control	21 (2.00±3.59)	21 (2.33±3.69)	21 (0.33±3.03)	
HI (events/h)	HOT	21 (7.76±3.62)	21 (1.08±1.39**)	21 (−6.69±3.54)	<0.001
	Control	21 (8.53±5.17)	21 (7.09±5.16)	21 (−1.44±3.57)	
ODI (dips/h)	HOT	21 (20.47±9.88)	21 (5.16±4.50**)	21 (−15.31±9.69)	<0.001
	Control	21 (20.23±10.07)	21 (21.93±13.01)	21 (1.70±12.85)	
Mean SpO_2 (%)	HOT	21 (95.1±1.8)	21 (98.1±0.9**)	21 (3.0±1.6)	<0.001
	Control	21 (94.8±1.6)	21 (94.2±1.9)	21 (−0.6±1.7)	
Blood gas					
$PaCO_2$ (mmHg)	HOT	21 (37.11±4.20)	21 (39.51±3.76*)	21 (2.40±4.63)	0.941
	Control	21 (38.10±4.56)	21 (39.70±3.80)	21 (1.60±6.15)	
Holter recording during sleep					
Mean HR (beats/min)	HOT	21 (68.2±8.1)	21 (65.1±7.8)	21 (−3.1±9.6)	0.436
	Control	21 (64.8±8.2)	21 (64.5±10.7)	21 (−0.3±5.3)	
Quality of life					
Specific Activity Scale (Mets)	HOT	24 (3.94±1.18)	24 (4.75±1.59**)	24 (0.82±1.17)	0.009
	Control	23 (3.98±1.08)	23 (3.87±1.24)	23 (−0.11±0.73)	
Echocardiography					
LVEF (%)	HOT	21 (33.04±8.91)	21 (38.49±15.46*)	21 (5.45±11.94)	0.223
	Control	21 (31.75±7.59)	21 (33.02±11.16)	21 (1.28±9.77)	
Blood marker					
BNP (pg/ml)	HOT	24 (492.8±434.7)	24 (555.7±556.1)	24 (62.9±335.3)	0.272
	Control	23 (410.4±445.4)	23 (386.8±453.9)	23 (−23.6±165.8)	
ANP (pg/ml)	HOT	24 (151.1±129.3)	24 (145.1±112.7)	24 (−6.0±85.1)	0.846
	Control	23 (121.8±101.6)	23 (125.4±122.1)	23 (3.6±57.5)	
NE (pg/ml)	HOT	24 (530.9±213.6)	24 (602.5±275.5)	24 (71.6±255.8)	0.631
	Control	23 (587.3±219.9)	23 (673.4±292.1)	23 (86.1±270.7)	

P values concern the comparison between the HOT and control groups by analysis of covariance or 2-way repeated measures analysis of variance (for specific activity scale). Mean±SD. *P<0.05, **P<0.01 compared with baseline with-in group by paired t-test.
SDB, sleep disordered breathing; CAI, central apnea index; OAI, obstructive apnea index; HI, hypopnea index; SpO_2, percutaneous arterial oxygen saturation; HR, heart rate. Other abbreviations see in Table 1.

primarily by the combined rate of cardiac death, hospitalization because of worsening HF and a decrease in the Specific Activity Scale by ≥1 Mets. The cardiac events were regularly reviewed under blindness to the assignation of patients by the Endpoint Classification Committee.

SDB Indicators

The patients who met the inclusion criteria were monitored by PSG or if that was not available, by a cardiorespiratory monitoring device (Morphase® [Somté], Compumedics Ltd, Victoria, Australia). Oronasal signals detected by thermistor were used as the respiratory sensors, thoracic and abdominal effort was measured by 2 belt sensors. SpO_2 was recorded by digital pulse oximetry (sampling frequency of 1 s). Surface lead ECG was also monitored throughout the night. The respiratory event detection and oximetry analysis were performed manually.

The oximeter signal quality of the cardiorespiratory monitoring device was proved to be valid in comparison with PSG[20,21] Apnea was defined as the absence of tidal volume for ≥10s, and hypopnea as a reduction of ≥50% in tidal volume from baseline for ≥10 s with oxygen desaturation of 3% from baseline[22] Standard definitions were used for OSA and CSA on the basis of the presence or absence of rib cage and abdominal excursions with an absence of airflow[22] The ODI was the number of times per hour that the oxyhemoglobin saturation fell by 4% and the apnea–hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour during the time in bed.

The arterial blood gas analysis was performed in the daytime after resting for at least 30 min to assess the arterial partial pressure of carbon dioxide ($PaCO_2$).

Assessment of QOL

We used the Specific Activity Scale as a measure of QOL in which self perceived exercise tolerance is expressed by an energy cost spent in the maximal physical activity that the patient can perform[23] The Specific Activity Scale allows expression of the extent of submaximal physical activity. We actually measured the metabolic costs of various types of physical activity by hooking subjects up to a mask to measure oxygen consumption and the volume of carbon dioxide exhaled. Then we prepared questionnaires about specific physical activities that a patient would perform either customarily or sporadically in daily life and each patient was asked to specify whether he/she could perform each type of activity without symptomatic limitation. Summarizing the questionnaire data, a given number of metabolic costs (Specific Activity Scale) were derived for each patient with regard to the self-perceived exercise tolerance. As a clear linear correlation was observed between Specific Activity Scale and peak oxygen consumption[23] the Specific Activity Scale was considered to reliably predict exercise capacity.

Ventricular Function

LVEF was followed up using 2-dimensional (D) echocardiography at rest during the daytime while patients were awake. The left ventricular (LV) end-diastolic and end-sys-

tolic volumes were determined according to a modification of Simpson's method. LVEF was calculated as end-diastolic minus end-systolic volume divided by end-diastolic volume.

Plasma Concentration of Neuropeptides

Venous blood samples were drawn through an indwelling catheter in the forearm of each patient after they had lain quietly and undisturbed for at least 30 min. Plasma was immediately separated and stored at −70°C before the norepinephrine (NE) concentrations were determined by high-performance liquid chromatography electrochemical detection. Plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) was determined by the chemiluminescent enzyme immunoassay.

Statistical Analysis

All statistical analyses were performed with SAS® version 9.1 (Cary, NC, USA). Results are mean±standard deviation (SD), unless otherwise indicated. The calculated sample size was based on assumption of 1-year cumulative incidence rates of 80% in the control group and a hazard ratio of 0.43. The cumulative incidence rates of the cardiac event were calculated by the Kaplan-Meier method in each group and compared by log-rank test. The hazard ratio was estimated by Cox's regression. For the Specific Activity Scale, repeated measures analysis of variance (ANOVA) with 2 factors (group and time) was applied. Changes in NYHA functional class were tested by Mann-Whitney U test. For the other parameters, analyses of covariance using a baseline value as a covariate were used to compare the difference between the control and HOT groups in response at the end of study. Paired t-tests were used to compare within-group data. Missing values were imputed using the Last-Observation-Carried-Forward approach without the data of the discontinuation, hence in the Specific Activity Scale; missing values were imputed with the mean value to just before discontinuation. A value of $P<0.05$ was considered statistically significant.

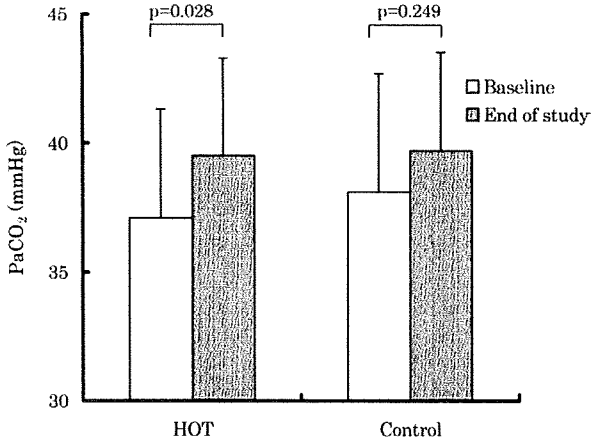


Figure 2. Change from baseline to the end of the study (52 weeks) of arterial partial pressure of carbon dioxide ($PaCO_2$). $PaCO_2$ increased in the home oxygen therapy (HOT) group (P=0.028 by paired t-test), but remained the same in the control group (P=0.249 by paired t-test). Mean±SD.

Results

Patient Characteristics

A total of 52 patients were enrolled from 19 centers: 26 were randomly assigned to treatment with HOT and the remaining 26 maintained normal breathing with conventional therapy. One patient in the control group dropped out before the start of the trial because of withdrawal of the consent. Accordingly, 26 patients in the HOT group and 25 patients in the control group were finally assessed.

The baseline characteristics of the patients are shown in **Table 1**. There were no significant differences between the groups with respect to any of the listed parameters. ODI and AHI were also similar in both groups. The mean treatment hours per night with oxygen were 8.15±1.86 h (range: 4.20–12.05 h). Thus, compliance with HOT did not appear to be disturbed by the procedure.

Effects of Supplemental Oxygen at Night on SDB

In the HOT group, supplemental oxygen for 52 weeks significantly improved SDB, AHI being reduced from 19.05±12.29 to 8.98±8.43events/h ($P<0.001$). Although suppression of OSA was not observed, CAI and HI were significantly decreased from 9.44±8.59 to 3.54±5.40 events/h ($P=0.002$) and from 7.76±3.62 to 1.08±1.39 events/h ($P<0.001$), respectively. ODI was significantly reduced from 20.47±9.88 to 5.16±4.50 dips/h ($P<0.001$) associated with an increase in mean SpO_2 from 95.1±1.8 to 98.1±0.9% ($P<0.001$) (**Figure 1**). These values remained unchanged in the control group. The differences between the HOT and the control groups were highly significant (**Table 2**).

Figure 2 shows the change of $PaCO_2$ from baseline to the end of the study (52 weeks) in the HOT and control

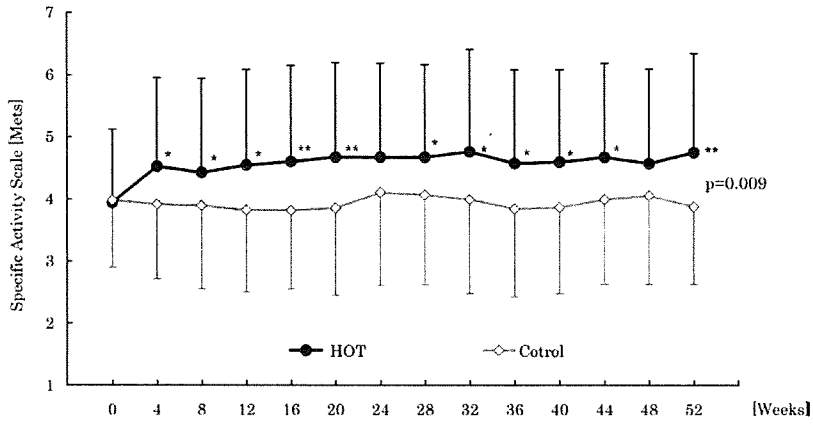


Figure 3. Time course of the Specific Activity Scale score. The Specific Activity Scale remained significantly augmented throughout the study period in the home oxygen therapy (HOT) group as compared with the control group (P=0.009 by repeated measures analysis of variance (ANOVA)). *P<0.05, **P<0.01 compared with the control group at the indicated time intervals by ANOVA. Mean±SD.

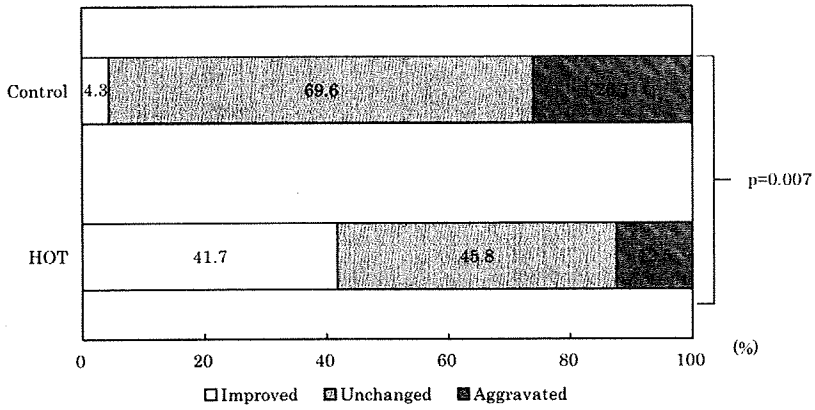


Figure 4. In the home oxygen therapy (HOT) group, the ratio of patients with an improvement in New York Heart Association functional class from baseline to the end of the study was significantly higher as compared with the control group (P=0.007 by Mann-Whitney U test). %.

groups. $PaCO_2$ increased from 37.11±4.20 to 39.51±3.76 mmHg in the HOT group (P=0.028), and from 38.10±4.56 to 39.70±3.80 mmHg in the control group. However, the latter change did not reach statistical significance (P=0.249).

Changes in the Specific Activity Scale

Figure 3 shows the time course of the Specific Activity Scale. There was no significant difference at baseline between the 2 groups (3.94±1.18 vs 3.98±1.08, P=0.903). Analysis of covariance using the baseline values as covariates revealed a significant overall improvement in the HOT group compared with the control group (P=0.009). The difference in the Specific Activity Scale between baseline (3.94±1.18 Mets) and 52 weeks (4.75±1.59 Mets) was significant in the HOT group (P=0.002) consistent with a treatment-related increase in daily physical activity. In contrast, the difference in the control group (3.98±1.08 to 3.87±1.24) was not statistically significant.

Changes in NYHA Functional Class

In the HOT group, NYHA functional class improved

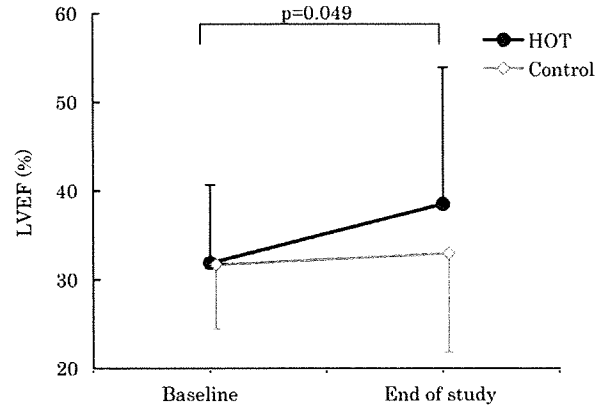
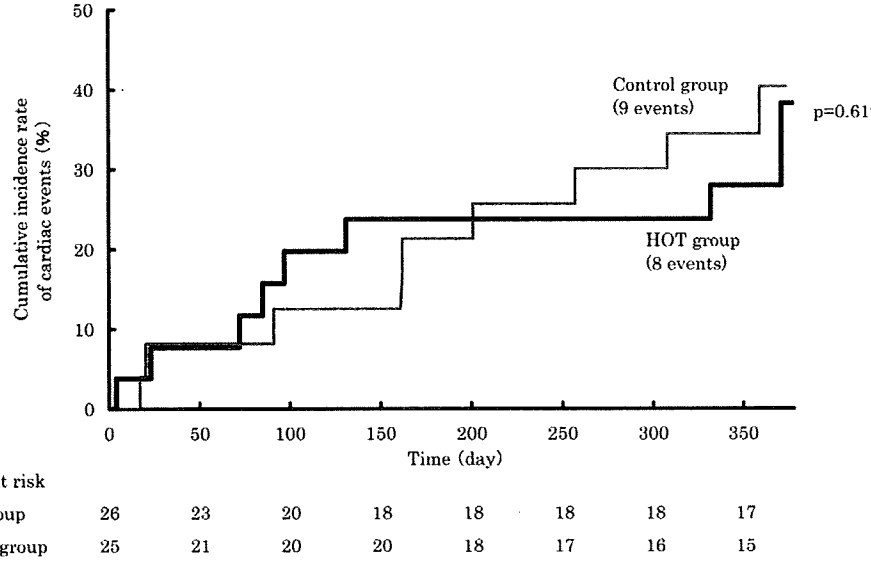


Figure 5. Left ventricular ejection fraction (LVEF) increased significantly from baseline to the end of the study in the home oxygen therapy (HOT) group (P=0.049 by paired t-test), but the change was not significant as compared with the control group (P=0.223 by analysis of covariance). Mean±SD.



Numbers at risk

HOT group	26	23	20	18	18	18	18	17
Control group	25	21	20	20	18	17	16	15

Figure 6. Kaplan-Meier estimations of cumulative incidence rates of cardiac events in the 2 groups. There was no statistical difference (hazard ratio for cardiac event, 0.78; P=0.619 by log-rank test) in the cumulative incidence rates of cardiac events between the home oxygen therapy (HOT) and control groups.

more (41.7%), and worsened less (12.5%), whereas in the control group, NYHA functional class improved less (only 4.3%) and worsened more (26.1%). The difference between the 2 groups was highly significant (P=0.007) (**Figure 4**).

Changes in LV Function

LVEF increased significantly from baseline to the end of the study (from 33.04±8.91 to 38.49±15.46%, P=0.049) in the HOT group, but there was no change in the control group (from 31.75±7.59 to 33.02±11.16%) (**Figure 5**). The changes in LVEF from baseline to 52 weeks were 5.45±11.94% in the HOT group, and 1.28±9.77% in the control group, but this difference did not reach statistical significance (**Table 2**).

Cardiac Events

During the 52-week study period, 1 patient died suddenly from arrhythmia and 7 were hospitalized for worsening HF in both groups. Continuous decrease in Specific Activity Scale was observed in 1 other patient in the control group. In the proportional hazards model, there was no difference in the cumulative incidence rate of cardiac events of the HOT group (38.3%) and the control group (40.4%) (hazard ratio for cardiac events 0.78; 95% confidence interval, 0.30–2.05; P=0.619 [log-rank test]). The lack of an event rate appears to be related to some unbalanced distribution in the severity of HF, though not statistically significant. The number of NYHA functional class III patients was 10 in the HOT group, and 5 in the control group, while Class II patients were 16 in the HOT group and 20 in the control group. Thus, more events were observed in the HOT group during the first 3 months, but this event rate was reversed after 3 months in favor of the HOT group (**Figure 6**).

Plasma BNP, ANP and NE Levels

After the 52-week oxygen therapy there were no obvious changes in the plasma NE, ANP, nor BNP levels in the blood samples obtained in the early morning after rest (**Table 2**).

Discussion

Although small randomized trials of short duration have demonstrated that nocturnal oxygen improves sleep quality in patients with HF and CSA[14,15,18] associated with a reduction in nocturnal sympathetic activity, there is no consistent evidence that oxygen therapy produces an improvement in cardiac function, QOL or clinical outcome of these patients?[24] In addition, supplemental oxygen has been suggested to cause hyperoxia, which can have an adverse effect on myocardial function because of the generation of oxygen free radicals?[25,26]

We previously conducted a prospective study to elucidate the efficacy of 12 weeks of nocturnal oxygen therapy using a conventional oxygen concentrator on ventricular function, severity of HF, and QOL, together with an improvement in SDB, in ambulatory patients with stable CHF and CSR![19] That study demonstrated that short-term treatment with nocturnal oxygen significantly improved NYHA functional class, Specific Activity Scale as a measure of QOL, and SDB in CHF patients with CSR-CSA; LVEF also increased from baseline to the end of the study. In the present study, we extended the follow-up period for 52 weeks and confirmed that long-term HOT was well tolerated and the benefit observed in the 12 week treatment was sustained over the longer period of time. Despite recent evidence that SDB has adverse effects on patients with CHF, only limited attention has been paid to it as a potential therapeutic target. Furthermore, there is no consensus as to the full range of indications for treatment of CSA;[27] there are many options for treatment of CSA, but only continuous positive airway pressure (CPAP) has been tested for survival. However, that trial was prematurely terminated because of increased early mortality of patients in the CPAP arm?[28] The failure of CPAP in improving outcome might be attributed to hemodynamic effects associated with an increase in intrathoracic pressure that could decrease venous return, adversely affecting right ventricular stroke volume, causing hypotension, decreased coronary blood flow, and myocardial ischemia?[29] In this regard, supplemental oxygen may not be associated with these adverse hemodynamic effects and could be more efficacious in improving prognosis.

In Western societies, the therapeutic goal of HF has been directed to reduce mortality; however, in Japan the severity of HF is relatively mild and mortality from heart disease is substantially lower?[30] Thereby QOL is considered more likely to be the primary goal of treatment. It has been shown that the prevalence of SDB is high, even in patients with milder symptomatic HF, because of LV systolic dysfunction?[31] QOL is substantially impaired by SDB, and HF patients with CSR-CSA have a worse QOL than those with CHF alone?[32] In Japanese studies of HF, the Specific Activity Scale is frequently used as a measure of QOL because it has been shown to reliably predict exercise capacity and physical activity in daily life?[23] The present study confirmed in the setting of a randomized trial that sustained treatment with nocturnal oxygen over 12 months produced a continuous rise in the Specific Activity Scale in patients with CHF and CSR-CSA, in conjunction with an improvement in sleep quality.

After the initial 12 week study, we carried out a questionnaire survey of physicians who participated in the previous study regarding the morbid events in those who continued HOT for more than 6 months. In those patients, frequencies per year of hospitalization and emergency visits were reduced to approximately one-fourth. Accordingly, cost savings of 51% were achieved, even including the cost of using the oxygen concentrator?[33] Although there were no differences in the overall event rates between the HOT and control groups in the present study, the lack of statistical significance for this comparison may reflect low study power rather than a lack of difference in the event rate between the groups. This is attributed to the small sample size and the greater proportion of patients with more severe HF (NYHA functional class III, 10 vs 5) and the smaller proportion of less severe HF patients (NYHA functional class II, 16 vs 20) in the treatment arm as compared with the control group, though this difference was not statistically significant. This disparity between groups caused divergence of the event rates in the first 3 months; more events occurred in the patients randomized to HOT than in the control group (5 vs 3), but the event rate was reversed after 3 months to favor the HOT group (3 vs 6).

As in the previous short-term study, nasal oxygen therapy failed to produce changes in plasma natriuretic peptides in the present study, presumably because of its modest effect on sleep apnea, the AHI being reduced only from 19 to 9. Staniforth et al also reported that oxygen had no effect on natriuretic peptides in either early morning serum or overnight urine![18] Those authors postulated that the arousal stimulus in CSR is the large negative deflections in intra-

thoracic pressure seen during periods of hyperpnea, rather than the mild degree of hypoxia associated with CSA. Although carbon dioxide improves CSR by reducing underdamping and offsetting the detrimental effects of periods of hypoxia on oxygen hyperresponsiveness, it cannot restore the underlying level of damping and controller gain back to normal and is unable to stabilize breathing sufficiently to reduce the number of arousals to below that critical level at which sleep architecture is normalized. The lack of changes in plasma NE levels in the present study may also be explained by the short half-life of catecholamines, not remaining elevated once disordered breathing has ceased.[18]

The mechanisms by which CSA is reduced by oxygen are multifactorial. Hanley's group suggested that prolonged circulation time between the carotid body and the lung causes a delayed response of the arterial and central chemoreceptors to variations in the arterial partial pressure of both oxygen (PaO_2) and carbon dioxide ($PaCO_2$), which results in overshooting in both directions and causes CSA in HF. Thereby, administration of oxygen improves CSA, by increasing both oxygen stores and arterial oxygen saturation, through damping the respiratory control system, reducing controller sensitivity and increasing arterial $PaCO_2$ above the apneic threshold.[14] Franklin et al reported on the basis of their observation of a large increase in PaO_2 and only a small increase in $PaCO_2$ during oxygen therapy that not only the increase in PaO_2 but also an increase in $PaCO_2$ eliminates apnea.[16]

Javaheri described 3 major therapeutic effects of oxygen therapy.[34] (1) A rise in $PaCO_2$ leading to a widening of the difference between the prevailing $PaCO_2$ and the $PaCO_2$ at the apneic threshold. When the difference between these 2 set points is wide, the occurrence of CSA is suppressed because a large ventilatory overshoot is necessitated to reduce $PaCO_2$ below the apneic threshold. (2) Suppression of the ventilatory response to hypercapnia. It has been suggested that enhanced sensitivity to carbon dioxide predisposes to the development of CSA. Normally, the rate and depth of breathing are regulated by a negative-feedback system to maintain the $PaCO_2$ within a narrow range throughout life. Therefore, the greater the sensitivity to carbon dioxide, the greater the ventilatory response and in some persons a large hyperventilatory response during sleep may lower the $PaCO_2$ below the apneic threshold, resulting in CSA. Reducing the sensitivity to carbon dioxide and the ventilatory response to hypercapnia by oxygen improves CSA by reversing this process. (3) Increasing the body stores of oxygen may buffer oscillations in blood gases with each apnea. The dampening the respiratory control system minimizes the change in PaO_2 for a given change in ventilation, making it more stable.

Although it has been widely accepted that CSA clearly has a negative effect on the clinical course of CHF, it remains uncertain whether CSR-CSA is an epiphenomenon of the failing heart or a major contributor to the poor outcomes of patients with CHF.[35] There is a growing body of evidence that intensive treatment for HF attenuates CSA.[10,36–38] The data suggest that CSA is likely to be secondary to CHF and could be resolved by optimization of HF therapy. However, in other cases, successful treatment of HF has not been associated with an improvement in CSR-CSA.[39–41] In such patients, breathing control centers could be permanently damaged, and optimization of hemodynamics and cardiac function by effective therapies for HF appear to have no major effect on SDB, CSA remaining common in CHF patients despite advances in medical therapy. CSR-CSA does not appear to be a simple reflection of severely compromised cardiac function,[10] but exerts unique and independent pathologic effects on the failing myocardium.[42] Therefore, CSR-CSA may still represent a potential target of therapy for the persistently symptomatic patient on optimal medical therapy.[43]

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Appendix 1

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Clinical significance of left ventricular hypertrophy and changes in left ventricular mass in high-risk hypertensive patients: a subanalysis of the Candesartan Antihypertensive Survival Evaluation in Japan trial

Shinji Yasuno[a], Kenji Ueshima[a], Koji Oba[a], Akira Fujimoto[a], Toshio Ogihara[b], Takao Saruta[c] and Kazuwa Nakao[a,d]

Objective To evaluate the associations of left ventricular hypertrophy (LVH) and its changes with the incidence of cardiovascular events and the time-course of serum creatinine (sCr) levels in high-risk hypertensive patients who participated in the Candesartan Antihypertensive Survival Evaluation in Japan trial.

Methods We analysed data of 1447 patients who underwent echocardiography at enrolment as an observational study irrespective of allocation. According to the left ventricular mass index (LVMI) at the baseline, they were divided into two groups (without LVH, LVMI $< 125\,g/m^2$; $n = 607$ and with LVH, LVMI $\geq 125\,g/m^2$; $n = 840$) and four categories on the basis of LVMI at the baseline and 1 year: absence of LVH ($n = 285$), development of LVH ($n = 97$), regression of LVH ($n = 155$), and persistence of LVH ($n = 418$).

Results During 3.3 ± 0.8 years, cardiovascular events occurred in 20 (3.3%) patients without LVH and in 67 (8.0%) patients with LVH (hazard ratio: 2.58; 95% confidence interval: 1.54–4.33; $P < 0.001$). Among the four categories, absence of LVH was associated with lower risk of cardiovascular events than persistence of LVH (hazard ratio: 0.30; 95% confidence interval: 0.13–0.71; $P = 0.006$), but development or regression of LVH was not. Only in persistence of LVH did the sCr level significantly increase over time (baseline vs. 3 years; 0.92 vs. 1.02 mg/dl, $P < 0.001$). Adjusted sCr level of absence and regression of LVH at 3 years was significantly lower than that of persistence of LVH (0.89 and 0.90 vs. 0.97 mg/dl, $P < 0.001$, $P = 0.002$, respectively), but that of development of LVH was not.

Conclusion Protection against LVH is associated with a reduced risk of cardiovascular events and may be related to the preservation of renal function in high-risk hypertensive patients. *J Hypertens* 27:1705–1712 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: cardiovascular events, echocardiography, hypertension, left ventricular hypertrophy, serum creatinine, target organ damage

Abbreviations: ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; LV, left ventricular; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; sCr, serum creatinine; TOD, target organ damage

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Introduction

Hypertension is a major risk factor for cardiovascular events because of its effect on several target organs, including the brain, heart and kidney [1]. Recently, the development of new class of antihypertensive drugs has enabled us not only to control blood pressure (BP) adequately, but also to choose preferred drugs depending on each patient's condition, resulting in a reduction in the rate of cardiovascular in hypertensive patients [2,3]. However, the cardiovascular events rate is still high in hypertensive patients who have already suffered target organ damage (TOD). Considering this, it is very important to assess and manage both the risk factors and TOD in the treatment strategy for hypertension in addition to adequate BP control [4,5].

Recently, investigators have tried to predict cardiovascular events by evaluating early and possibly reversible signs of TOD. Left ventricular hypertrophy (LVH) is one of the manifestations of TOD in hypertensive patients. It is generally accepted that LVH is strongly associated with the risk of cardiovascular events, including ischemic heart disease, congestive heart failure, stroke, renal disease, vascular disease and sudden death [6–10]. Furthermore, recent interventional studies have suggested that maintenance of normal left ventricular (LV) mass or regression of LVH during antihypertensive treatment lead to a reduction in the cardiovascular events rate in uncomplicated hypertensive patients [11–13]. However, there is little evidence for the associations of LVH and the changes in LV mass with the incidence of cardiovascular

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events and other TOD in the specific setting of high-risk hypertensive patients [14].

The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial was designed to compare the long-term effect of the angiotensin II receptor blocker (ARB) candesartan cilexetil and the calcium channel blocker (CCB) amlodipine besylate on the incidence of cardiovascular events represented as a composite of sudden death, cerebrovascular, cardiac, renal and vascular events in 4728 high-risk Japanese hypertensive patients [15]. BP was controlled to levels as low as 140/80 mmHg in both treatment groups. There was no statistically significant difference in primary cardiovascular events between the two groups.

In the present study, we focused on the 1447 high-risk hypertensive patients who underwent echocardiography at enrolment. We analysed their data as an observational study irrespective of allocation. The first goal was to verify the prognostic value of LVH determined at echocardiography for cardiovascular events. The second goal was to evaluate the associations of the changes in LV mass with the incidence of cardiovascular events and the time-course of serum creatinine (sCr) levels as another manifestation of TOD.

Methods

Study design and treatment schedule in the Candesartan Antihypertensive Survival Evaluation in Japan trial

The CASE-J trial was a prospective, multicentre, randomized, open-label, active-controlled, two-arm parallel-group comparison study to evaluate the efficacy of ARB candesartan and CCB amlodipine for reducing the incidences of cardiovascular events in high-risk Japanese hypertensive patients [15]. The Ethics Committee at Kyoto University Graduate School of Medicine approved the CASE-J trial protocol according to the principles of the Helsinki Declaration. Written informed consent was obtained from each participating patient before allocation. The rationale and complete design of the CASE-J trial has been previously reported [16]. Briefly, 4728 patients with high-risk hypertension were randomly assigned to either candesartan-based or amlodipine-based treatment regimens. High-risks were defined as the presence of any one of the following factors: severe hypertension: systolic BP (SBP) more than or equal to 180 mmHg and/or diastolic BP (DBP) $\geq$ 110 mmHg; type 2 diabetes mellitus; a history of stroke or transient ischemic attack more than 6 months prior to the screening; LVH, angina pectoris, or a history of myocardial infarction more than 6 months prior to the screening; proteinuria or sCr more than or equal to 1.3 mg/dl and arteriosclerotic peripheral artery obstruction. The exclusion criteria were also reported elsewhere [16]. Enroled patients were given one of the following medications after randomization, candesartan was administered orally at a dose of 4–12 mg/day, and amlodipine was administered orally at a dose of 2.5–10 mg/day. The BP targets were determined according to the guideline proposed by the Japanese Society of Hypertension [17].

Echocardiography and definition of left ventricular hypertrophy

Certified examiners in each institute who participated in the CASE-J trial performed echocardiography. Echocardiographic study was carried out in 1447 patients at enrolment and 955 (66%) of them 1 year after allocation. Two-dimensional guided M-mode echocardiography was performed and the following echocardiographic parameters were measured: end-diastolic LV internal diameter (LVIDd), end-diastolic interventricular septal thickness and end-diastolic LV posterior wall thickness (PWTd). LV mass was calculated according to the following formula introduced by Devereux *et al.* [18], normalized by body surface area and expressed as left ventricular mass index (LVMI) (g/m^2):

$$\text{LV mass (g)} = 0.8 \times 1.04 \times [(\text{IVSTd} + \text{LVIDd} + \text{PWTd})^3 - \text{LVIDd}^3] + 0.6$$

According to the presence or absence of LVH (LVMI $\geq 125\ g/m^2$) at the baseline, we separated the 1447 patients into the two groups (without LVH at the baseline; $n = 607$, with LVH at the baseline; $n = 840$), because LVMI more than or equal to $125\ g/m^2$ was considered to be the cut-off point of LVH in several other studies [6,8,9,12].

One year after treatment, echocardiography was performed in 382 patients without LVH at the baseline and 573 patients with LVH at the baseline. We also divided the 955 patients into four categories on the basis of LVMI at the baseline and 1 year: absence of LVH ($n = 285$), development of LVH ($n = 97$), regression of LVH ($n = 155$) and persistence of LVH ($n = 418$).

Outcome measurements

The primary endpoint was the first fatal/nonfatal cardiovascular event (a composite of sudden death, which is unexpected death that occurs within 24 h without external causes; cerebrovascular events including stroke or transient ischemic attack; cardiac events including heart failure, angina pectoris, or acute myocardial infarction; renal events including sCr more than or equal to 4.0 mg/dl, doubling of the sCr (however, sCr $\leq$ 2.0 mg/dl is not regarded as an event), or end-stage renal disease; and vascular events including dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery. We also examined the time-course of sCr level every 6 months from the baseline up to 3 years.

The event evaluation was performed independently by the Event Evaluation Committee, which was blinded to

the assigned treatment groups and adjudicated according to the protocol criteria. A diagnosis for each cardiovascular event was determined by the Event Evaluation Committee using the predefined criteria.

Statistical analysis

Data are expressed as the mean ± standard deviation (SD) or proportions. We compared continuous variables using the Student's *t* test between the two groups and analysis of variance among groups. Frequency analysis was performed by chi-square test. Risk-adjusted cumulative incidence of cardiovascular events was calculated using the corrected group prognosis method [19] with adjustment for baseline characteristics, including a history of prior antihypertensive treatment, allocated drugs, age, sex, body mass index (BMI), type 2 diabetes, a history of cerebrovascular disease, a history of ischemic heart disease, renal dysfunction, a history of vascular disease, and SBP and DBP at the baseline. The hazard ratio and 95% confidence intervals were estimated using the multiple Cox regression analysis adjusted for baseline characteristics (a history of prior antihypertensive treatment, allocated drugs, age, sex, BMI, type 2 diabetes, a history of cerebrovascular disease, a history of ischemic heart disease, renal dysfunction, and a history of vascular disease) as standard covariates (model 1), and baseline and subsequent BP and additional drugs (diuretics, α-blockers and β-blockers) during the trial as time-varying covariates in addition to baseline characteristics (model 2). When we evaluated the time-course of sCr levels, we performed a mixed-effect linear regression (PROC MIXED in SAS version 9.1) to account for non-independence of the same subjects, and adjusted for possible baseline confounders (a history of prior antihypertensive treatment, allocated drugs, age, sex, BMI, type 2 diabetes, a history of cerebrovascular disease, a history of ischemic heart disease, renal dysfunction, and a history of vascular disease). We examined the association of the changes in LVMI with the time-course of sCr levels after adjusting subsequent variables to the baseline (SBP, DBP, diuretics use, α-blocker use, and β-blocker use during follow-up) as time-dependent covariates in addition to the baseline confounders. Point estimates of the sCr value at each time represent least-square means. The estimates and standard error were calculated from the mixed-effect linear regression. All statistical tests were two-sided with an α level of 0.05, and were performed using the SAS version 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Baseline characteristics

Of the 4728 patients in the CASE-J trial, 1447 patients who underwent echocardiography at the baseline were included in this analysis. Table 1 shows the baseline characteristics of the present study patients divided in two groups according to the presence or absence of LVH at the baseline. There were statistical differences between the dichotomized groups in the use of allocated drugs, the sex ratio, DBP, heart rate, BMI, sCr, and proportions of comorbidities. At the time of randomization, 417 (68.7%) of patients without LVH at the baseline and 588 (70.0%) of those with LVH at the baseline were treated with antihypertensive drugs (CCB; 38.6% vs. 43.5%, $P=0.061$, angiotensin-converting enzyme inhibitor; 18.0% vs. 16.2%, $P=0.377$, ARB; 18.6% vs. 18.2%, $P=0.846$, diuretics; 2.8% vs. 4.0%, $P=0.204$, β-blocker; 10.5% vs. 13.3%, $P=0.109$, α-blocker; 6.9% vs. 7.6%, $P=0.614$, αβ-blocker; 4.6% vs. 4.8%, $P=0.895$, respectively).

Table 1 Baseline characteristics of the study patients on the basis of LVMI at the baseline

Characteristics	Without LVH	With LVH
No. of participants	607	840
Prior antihypertensive treatment	417 (68.7)	588 (70.0)
Candesartan*	275 (45.3)	432 (51.4)
Age (years)	63.8 ± 10.5	64.1 ± 10.7
Men*	332 (53.0)	530 (63.1)
BMI (kg/m^2)*	24.3 ± 3.7	24.9 ± 3.5
SBP (mmHg)	160.8 ± 14.6	161.4 ± 14.1
DBP (mmHg)*	90.1 ± 10.6	91.4 ± 10.1
Heart rate (beats/min)*	72.2 ± 11.6	69.8 ± 11.3
Serum creatinine (mg/dl)*	0.87 ± 0.23	0.92 ± 0.29
LVMI (g/m^2)*	101.2 ± 17.3	168.7 ± 40.7
Severe HT (SBP ≥ 180 and/or DBP ≥ 110 mmHg)*	105 (17.3)	112 (13.3)
Type 2 diabetes*	256 (42.2)	256 (30.5)
Cerebrovascular disease		
Cerebral haemorrhage	13 (2.1)	13 (1.5)
Cerebral infarction*	58 (9.6)	32 (3.8)
TIA	4 (0.7)	7 (0.8)
Ischemic heart disease		
Angina pectoris	76 (12.5)	81 (9.6)
Old MI	66 (10.9)	85 (10.1)
Renal dysfunction		
Proteinuria	80 (13.2)	142 (16.9)
S-Cr ≥ 1.3 mg/dl*	33 (5.4)	82 (9.8)
Vascular disease		
ASO*	11 (1.8)	4 (0.5)

Data are shown as number of patients (%) or mean ± SD. ASO, atherosclerosis obliterans; BMI, body mass index; DBP, diastolic blood pressure; HT, hypertension; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; MI, myocardial infarction; SBP, systolic blood pressure; sCr, serum creatinine; TIA, transient ischemic attack. * $P<0.05$; Without LVH vs. With LVH.†Type 2 diabetes mellitus was defined by fasting blood glucose ≥126 mg/dl, casual blood glucose ≥200 mg/dl, HbA1c ≥ 6.5%, 2 h blood glucose on 75 g oral glucose tolerance test (OGTT) ≥200 mg/dl, or current treatment with a hypoglycemic agent at the baseline.

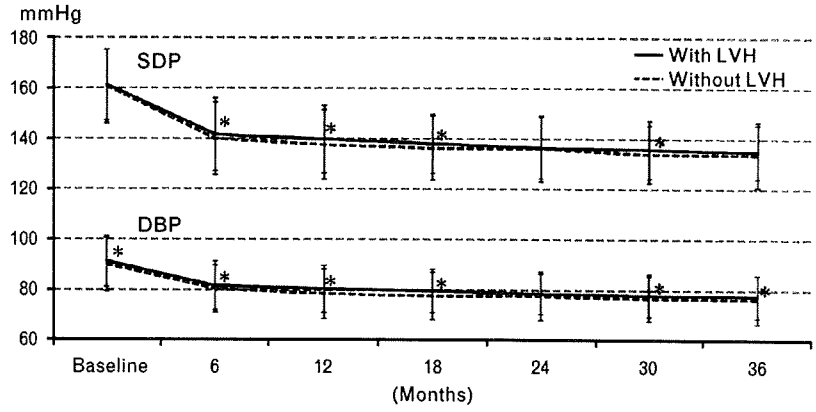
Changes in blood pressure

BP was controlled to levels as low as 140/80 mmHg in the two groups, but both SBP and DBP were slightly, but significantly, higher in the patients with LVH than those without LVH at the baseline (Fig. 1).

Prognostic value of left ventricular hypertrophy for the cardiovascular events rate

During 3.3 ± 0.8 years of follow-up, cardiovascular events occurred in 20 (3.3%) patients without LVH at the baseline for a rate of 10.0 per 1000 patient-years and in 67 (8.0%) patients with LVH at the baseline for a rate of 24.9 per 1000 patient-years. Cumulative incidence of cardiovascular events adjusted for baseline characteristics demonstrated that LVH was associated with the risk of

Fig. 1



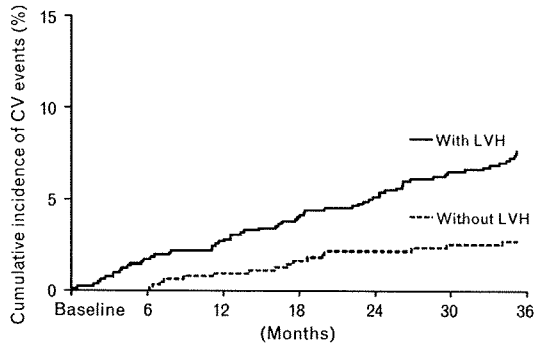
Systolic BP and diastolic BP measured in patients without left ventricular mass at the baseline and with left ventricular mass at the baseline during the follow-up period. LVH, left ventricular hypertrophy. Data are shown as mean ± SD. *$P < 0.05$, vs. without left ventricular mass.

cardiovascular events (hazard ratio: 2.59; 95% confidence interval: 1.55–4.34; $P < 0.001$, Fig. 2). The multiple Cox regression analysis in the two models revealed that LVH was an independent and powerful predictor for cardiovascular events, as well as diabetes, a history of cerebrovascular and ischemic heart disease, and renal dysfunction (Table 2). In addition, we evaluated the prognostic value of LVH for each event category. As shown in Fig. 3, LVH was strongly associated with the risk of cardiovascular death, cerebrovascular events and congestive heart failure.

Associations of the changes in left ventricular mass index with cardiovascular events and the time-course of serum creatinine levels

One year after treatment, echocardiography was performed in 382 patients without LVH at the baseline and in 573 patients with LVH at the baseline. Of 382 patients, 285 (74.6%) maintained LVMI less than 125 g/m^2, and of 573 patients, 155 (27.0%) achieved regression of LV mass (LVMI < 125 g/m^2). There were statistical differences among the four categories in age, the sex ratio, DBP, heart rate, sCr, and proportions of comorbidities (Table 3). In Fig. 4, cumulative incidence of cardiovascular events adjusted for baseline characteristics is shown among the four categories. Crude cardiovascular events rate (per 1000 patient-years) was 7.1 in patients with absence of LVH, 18.9 with development of LVH, 25.3 with regression of LVH, and 22.2 with persistent LVH. As shown in Table 4, absence of LVH was associated with a lower risk of cardiovascular events than persistent LVH. However, the risk of cardiovascular events in patients with development or regression of LVH did not differ from that in those with persistent LVH.

Fig. 2



The cumulative incidence of the primary composite endpoint adjusted for baseline characteristics in patients without left ventricular mass at the baseline and with left ventricular mass at the baseline. CV, cardiovascular; LVH, left ventricular hypertrophy.

In addition, we evaluated the time-course of sCr levels among the four categories as another manifestation of TOD. As shown in Fig. 5a, nonadjusted sCr level significantly increased only with persistent LVH over time (baseline vs. 3 years; 0.92 vs. 1.01 mg/dl, $P < 0.001$). Because there were statistical differences in baseline characteristics considered to affect the time-course of sCr among the four categories, we also examined the time-course of adjusted sCr level. As shown in Fig. 5b, the trend in each category was not changed and the adjusted sCr level of absence and regression of LVH at 3 years was significantly lower than that of persistence of LVH (0.89 and 0.90 vs. 0.97 mg/dl, $P < 0.001$, $P = 0.002$, respectively), but that of LVH development was not.

Discussion

The present study extended the clinical significance of LVH as a predictor for cardiovascular events in high-risk

Table 2 **Multiple Cox regression analysis for the predictors of cardiovascular events***

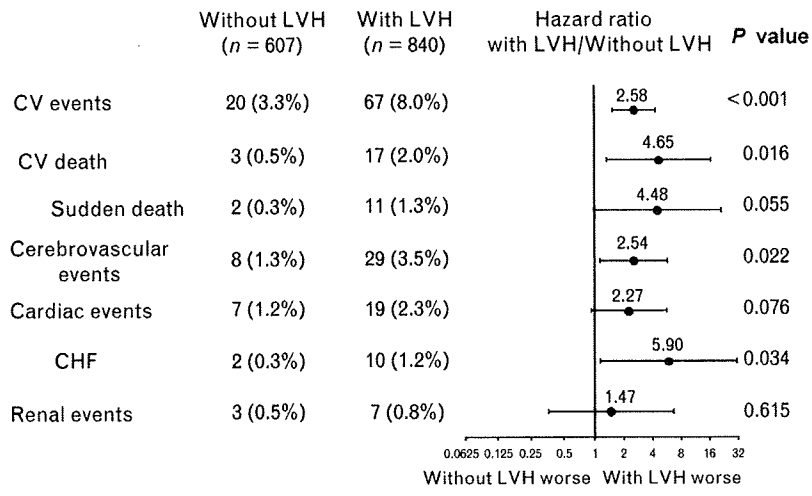
Variables	Model 1		Model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
LVH ($\geq$ 125 g/m^2)	2.59 (1.55–4.34)	<0.001	2.58 (1.54–4.33)	<0.001
Prior antihypertensive treatment, yes	1.11 (0.63–1.94)	0.719	0.98 (0.55–1.74)	0.950
Drug, candesartan	0.70 (0.46–1.08)	0.107	0.68 (0.44–1.05)	0.080
Age, per 10 year	1.19 (0.92–1.55)	0.191	1.25 (0.96–1.63)	0.094
Sex, male	1.13 (0.71–1.78)	0.612	1.06 (0.67–1.67)	0.802
BMI, per 1 kg/m^2	0.99 (0.93–1.06)	0.808	0.99 (0.92–1.05)	0.648
Diabetes, yes	1.97 (1.26–3.06)	0.003	2.08 (1.34–3.23)	0.001
Cerebrovascular disease, yes	2.22 (1.28–3.84)	0.004	2.27 (1.31–3.96)	0.004
Ischemic heart disease, yes	2.19 (1.39–3.44)	<0.001	2.13 (1.34–3.36)	0.001
Renal dysfunction, yes	2.82 (1.81–4.39)	<0.001	2.74 (1.74–4.30)	<0.001
Vascular disease, yes	2.38 (0.55–10.3)	0.243	2.25 (0.52–9.77)	0.278
SBP at the baseline, per 10 mmHg	1.12 (0.94–1.33)	0.221	–	–
DBP at the baseline, per 10 mmHg	0.76 (0.61–0.95)	0.016	–	–
Time-varying SBP, per 10 mmHg	–	–	1.14 (0.96–1.35)	0.139
Time-varying DBP, per 10 mmHg	–	–	0.83 (0.64–1.08)	0.160
Additional use of diuretics, yes	–	–	0.98 (0.54–1.76)	0.938
Additional use of β-blocker, yes	–	–	1.24 (0.76–2.03)	0.383
Additional use of α-blocker, yes	–	–	1.33 (0.79–2.24)	0.280

BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; LVH, left ventricular hypertrophy; SBP, systolic blood pressure. *Adjusted for each variable.

hypertensive patients. We demonstrated that LVH was an independent predictor for cardiovascular events, especially cerebrovascular events and congestive heart failure, in high-risk hypertensive patients as well as in uncomplicated hypertensive patients [6,8–13]. However, the reasons LVH is associated with the risk of cardiovascular events are not yet completely clear. Various mechanisms have been proposed to explain the relationship between LVH and cardiovascular events [20,21]. There may be two important concepts in the clinical implication of LVH. LVH has been considered predominantly as a valuable surrogate marker for cardiovascular events, reflecting longstanding exposure to volume and pressure overload, and representing the accumulation of risk factors, such as aging, obesity, diabetes, hypertension and so on, but it may also directly contribute to cardiovascular events, especially cardiac events and sudden death, through pathological changes in the heart [21,22].

We also assessed the association of the LVMI changes during antihypertensive treatment with the risk of cardiovascular events in high-risk hypertensive patients. Patients with absence of LVH were least likely to experience cardiovascular events among the four categories. Patients who developed LVH had a similar tendency to develop cardiovascular events to those with persistent LVH. In contrast to previous studies [11–14], we could not find that regression of LVH was associated with a reduction in subsequent cardiovascular events. There are several possible reasons for the discrepancy between the

Fig. 3



Results of the multiple Cox regression analyses for each event in patients without left ventricular mass at the baseline and with left ventricular mass at the baseline in model 2. CHF, congestive heart failure; CV, cardiovascular; LVH, left ventricular hypertrophy.

Table 3 **Baseline characteristics among the four categories**

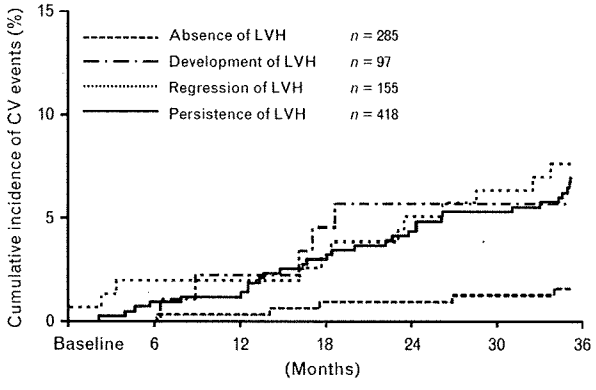
Characteristics	Absence	Development	Regression	Persistence
No. of participants	285	97	155	418
Prior antihypertensive treatment	200 (70.2)	71 (73.2)	105 (67.7)	316 (75.6)
Candesartan	131 (46.0)	41 (42.3)	84 (54.2)	223 (53.3)
Age (years)†	63.3 ± 10.4	65.2 ± 9.9	62.2 ± 10.9	65.3 ± 9.9
Men*	154 (54.0)	52 (53.6)	89 (57.4)	267 (63.9)
BMI (kg/m^2)	24.4 ± 3.7	24.7 ± 3.1	24.4 ± 3.5	25.0 ± 3.6
SBP (mmHg)	159.4 ± 14.4	164.0 ± 14.6	160.8 ± 15.3	160.7 ± 13.4
DBP (mmHg)†	89.6 ± 10.2	91.2 ± 11.6	92.4 ± 10.0	90.4 ± 9.5
Heart Rate (beats/min)†	72.0 ± 11.5	69.9 ± 11.5	72.8 ± 11.6	68.7 ± 10.5
Serum creatinine (mg/dl)†	0.85 ± 0.23	0.87 ± 0.25	0.92 ± 0.27	0.92 ± 0.29
LVMI (g/m^2)†	99.3 ± 17.5	110.1 ± 15.0	148.5 ± 26.5	176.6 ± 41.8
Severe HT*	40 (14.0)	21 (21.6)	25 (16.1)	40 (9.7)
Type 2 diabetes*	119 (41.6)	29 (29.9)	47 (30.3)	129 (30.9)
Cerebrovascular disease*	47 (16.5)	9 (9.3)	10 (6.5)	29 (6.9)
Ischemic heart disease*	77 (27.0)	27 (27.8)	29 (18.7)	82 (19.6)
Renal dysfunction*	46 (16.1)	15 (15.5)	31 (20.0)	95 (22.7)
Vascular disease	5 (1.8)	0 (0.0)	1 (0.6)	2 (0.5)

Data are shown as number of patients (%) or mean ± SD. BMI, body mass index; DBP, diastolic blood pressure; HT, hypertension; LVMI, left ventricular mass index; SBP, systolic blood pressure. † $P < 0.05$ by ANOVA. * $P < 0.05$ by χ^2 test among the four categories.

results of the present study and those of previous reports. First, the follow-up period may not have been long enough to observe the relation between regression of LVH and a reduction in the cardiovascular events rate. Second, the achieved BP level in this study was lower than that reported in previous studies [23]. Thus, there may be no difference in the cardiovascular events rate between regression of LVH and persistence of LVH under strict BP control. Finally, our entire study population was Japanese. Because the mortality of ischemic heart disease in Japan is one third of that in the United States [24], this low incidence of cardiovascular events may have affected our results.

In addition, we demonstrated associations between changes in LVMI and the time-course of the sCr level. It is well known that renal function is an important determinant of LVH [25]. In the present study, the actual value of sCr at the baseline was significantly higher in patients with LVH than those without LVH. Meanwhile, looking at Fig. 5a and b, the changes in LVMI preceded those of sCr. Furthermore, despite no differences in renal function at the baseline between regression and persistence of LVH, the sCr level decreased only in patients with LVH regression. From these results, we speculated that factors other than renal function, which we could not determine in the present study, contributed to the LVM changes. Previous studies reported that the decline in renal function could be influenced by a concentric pattern of LV remodelling [26]. In addition, higher urinary albumin excretion has been observed in patients with LVH [27–29], suggesting that cardiac and glomerular vascular damage may occur concurrently. Systemic inflammation and endothelial damage are possible mechanisms in the relation between them [30]. In the present study, there was a possibility that improvement in a common factor resulted in an action that was favourable for both LVH and renal function. Furthermore, duration of high blood pressure in patients with absence and regression of LVH may have been shorter than in those with persistence of LVH. In those patients, improvement in renal function could be anticipated under adequate BP control.

Fig. 4



The cumulative incidence of the primary composite endpoint adjusted for baseline characteristics among the four categories. CV, cardiovascular; LVH, left ventricular hypertrophy.

There were several limitations in the present study. First, this analysis was post hoc. The number of patients in each category may not have been high enough to examine the relations between change in LV mass and the cardiovascular events rate. Second, as mentioned above, the follow-up period may not have been long enough to observe the relation between regression of LVH and a reduction in the cardiovascular events rate. The CASE-J trial has been extended for 3 years as an observational study called CASE-J Ex. The CASE-J Ex may resolve this issue in the future. Third, since the echocardiograms were evaluated not centrally, but locally, we did not assess inter-observer variability. But, all the participating institutes specialized

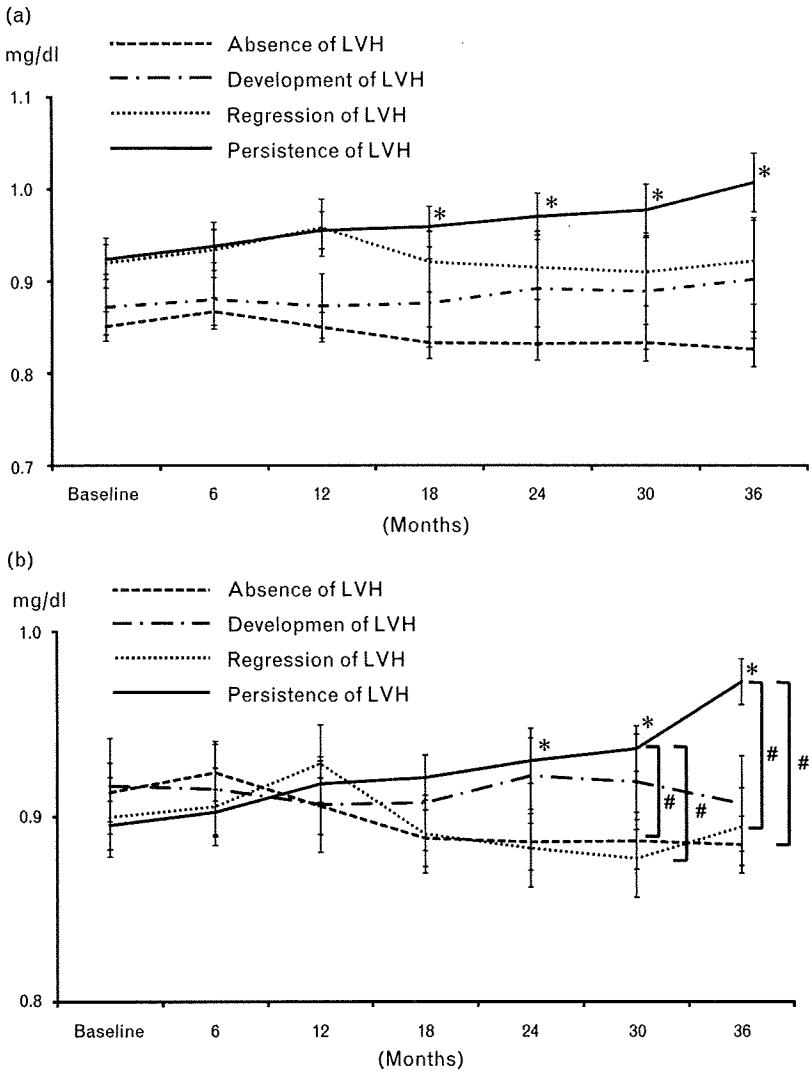
Table 4 cardiovascular events rate and hazard ratio among the four categories

LVH	CV events rate (per 1000 patient-years)	Model 1		Model 2	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Absence	7.1	0.28 (0.12–0.66)	0.004	0.30 (0.13–0.71)	0.006
Development	18.9	0.99 (0.41–2.41)	0.981	1.02 (0.42–2.48)	0.968
Regression	25.3	1.19 (0.61–2.33)	0.612	1.21 (0.62–2.36)	0.575
Persistence	22.2	1	–	1	–

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LVH, left ventricular hypertrophy. *HR of persistence of LVH for cardiovascular events was assigned a value of 1.0.

in cardiology and experienced examiners performed echocardiography, the same patients were followed up in the same institutes, because only patients with sinus rhythm were enroled, echocardiographic evaluation seemed to be stable. Accordingly, we think that echocardiographic data are relatively reliable for analysis. Finally, although the definition of LVH with a cut-off point of LVMI 125 g/m^2 is supported by several previous examinations, some investigators proposed different LVMI cut-off points. We also performed a separate

Fig. 5



(a) The time-course of nonadjusted serum creatinine levels among the four categories. (b) The time-course of adjusted serum creatinine levels among the four categories. LVH, left ventricular hypertrophy. Data are shown as mean ± SE. *$P < 0.05$ vs. baseline, #$P < 0.05$ vs. Persistence of left ventricular mass.

analysis in which the cut-off points of LVMI were 125 g/m^2 in males and 110 g/m^2 in females and similar results were obtained (data not shown).

In conclusion, LVH is an independent predictor for cardiovascular events in high-risk hypertensive patients and maintenance of normal LV mass during antihypertensive treatment is associated with a reduced risk of cardiovascular events. In addition, our study suggests that changes in LV mass are associated with those of renal function. Further studies are required to determine whether regression of LVH during antihypertensive treatment is a good surrogate marker to predict a reduction in subsequent cardiovascular events in the specific setting of high-risk hypertensive patients.

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ORIGINAL ARTICLE

Prognostic value of myocardial perfusion SPECT images in combination with the maximal heart rate at exercise testing in Japanese patients with suspected ischemic heart disease: a sub-analysis of J-ACCESS

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Abstract
Objectives We assessed whether a combination of summed stress scores (SSS) using exercise myocardial perfusion SPECT (Ex-SPECT) and maximal heart rate accurately predicts cardiac events through a sub-analysis of J-ACCESS (Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT) which was conducted to evaluate the prognosis of Japanese patients with suspected ischemic heart disease.
Methods In J-ACCESS, 2,373 patients with suspected coronary artery disease not receiving beta-blocker treatment underwent Ex-SPECT. These patients were categorized into the following four groups: Group A [achieved target heart rate (THR) and SSS < 4: $n = 631$], B (did not achieve THR and SSS < 4: $n = 612$), C (achieved THR and SSS ≥ 4: $n = 570$), and D (did not achieve THR and SSS ≥ 4: $n = 560$). We evaluated the incidence rate of cardiac events including cardiac death, myocardial infarction, and heart failure requiring hospital admission during a 3-year period.
Results In Group A, B, C, and D, 9 of 631 (1.4%), 15 of 612 (2.4%), 23 of 570 (4.0%) and 30 of 560 (5.4%) patients experienced cardiac events, respectively. Although the hazard ratio of the SSS ≥ 4 was 2.45 ($p < 0.001$) and that of the attained THR was 0.69 ($p = 0.10$) in the multiple Cox regression analysis, Kaplan–Meier curves showed that the cardiac events rate was lower in the order of A, B, C, and D ($p < 0.001$).
Conclusion The combination of SSS using Ex-SPECT and the maximal heart rate is a useful predictor of cardiac events in patients with suspected coronary artery disease.

Keywords Cardiac events · Exercise test · SPECT · J-ACCESS

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Introduction

Nuclear medicine guidelines in the USA have approved prognostic evaluation with myocardial perfusion SPECT and recognize the additional value of gated studies [1]. Although the prognostic values of both normal and abnormal SPECT findings in terms of event rates per year have been described, a large-scale investigation has not been conducted in a Japanese population. Accordingly, a multicenter study was conducted to establish a Japanese database called the Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT