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Original article

Efficacy and safety of a 60-week treatment with candesartan in Japanese patients with mild to moderate chronic heart failure

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ABSTRACT

Background: Chronic heart failure (CHF) is an increasingly common cardiovascular disease despite recent advances in its diagnosis and management.
Methods and results: A multicenter, open-label study was designed to assess the efficacy and safety of 60-week treatment with candesartan in Japanese patients with mild to moderate CHF. Primary efficacy endpoints were changes from baseline in plasma brain natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), end-diastolic dimension, and New York Heart Association (NYHA) functional class. Two hundred and eighty-nine eligible patients were divided into 2 groups based on the daily dose at the end of treatment: high-dose (HD, 8 mg, $N = 170$) and low-dose (LD, 2 or 4 mg, $N = 119$). Neither plasma BNP levels nor LVEF changed from the baseline to the end of treatment in the LD group, whereas BNP significantly improved from 61.6 to 50.1 pg/mL ($p = 0.0005$) and LVEF from 57.2 to 60.1% ($p = 0.0005$) in the HD group. The changes in NYHA functional class were comparable between groups: 21.2% improved and 76.3% unchanged in the LD group and 20.6% improved and 79.4% unchanged in the HD group. No safety concerns were observed in either group.
Conclusions: HD candesartan was more effective in improving plasma BNP levels and cardiac function than LD in Japanese CHF patients. Both LD and HD candesartan were well tolerated in CHF patients.

Introduction

Chronic heart failure (CHF) is an increasingly common cardiovascular disease and is the major cause of morbidity and mortality throughout the world [1–3]. Patients with CHF are at high risk for death and hospitalization for worsening HF. In Japan, approximately 1–2 million adults have CHF and more than 180,000 patients die of heart diseases each year with a death rate of approximately 140 per 100,000 persons [4].

For the treatment of hypertension and HF, angiotensin-converting-enzyme (ACE) inhibitors have been widely used as first-line drugs [1,2]. Angiotensin II receptor blockers (ARBs) have emerged as an alternative for inhibiting the renin–angiotensin–aldosterone system by selectively blocking the angiotensin II type 1 receptor. Candesartan is an ARB having a long-acting antihypertensive effect due to its lower dissociation rate from the angiotensin type 1 receptor [5].

A randomized, double-blind, placebo-controlled Assessment of Response to Candesartan in HF in Japan (ARCH-J) study evaluating the efficacy and safety of 6-month treatment with candesartan 8 mg once daily in patients with congestive HF demonstrated that the incidence of confirmed progression of congestive HF was significantly lower in the candesartan group, especially in the subgroup of patients previously treated with ACE inhibitors, than in the placebo group (7.4% vs. 22.2%) with a risk reduction of 66.7% and a risk difference of −14.8% ($p < 0.001$) [6]. Based on these results, an additional indication for candesartan for the treatment of mild to moderate CHF in patients for whom treatment with ACE inhibitors is inappropriate was approved in Japan in 2005.

In order to collect and analyze data on the frequency and background factors of dose escalation/reduction in a clinical setting, we conducted a study to assess the efficacy and safety of 60-week treatment with candesartan in Japanese patients with mild to moderate CHF.

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Subjects and methods

Study design

The study design is shown in Fig. 1. This study was a multicenter, open-label study consisting of a 4-week run-in period and a 60-week treatment period. The starting dose of candesartan for the treatment of CHF was 4 mg once daily, which could be increased up to 8 mg once daily as needed. An alternative starting dose of 2 mg once daily was recommended for a period not exceeding 4 weeks for patients who had systolic blood pressure (SBP) of <120 mmHg, renal dysfunction, severe HF, or those given diuretics concomitantly. All patients received candesartan, starting at a dose of either 2 or 4 mg once daily, which was increased to 8 mg once daily by week 12 as tolerated and needed. Dose escalation/reduction was decided upon as needed during the treatment period. Patients visited the study sites every 2–4 weeks (every 4 weeks in principle) from week −4 to week 60. Throughout the study period, concomitant medication for HF was allowed except for ACE inhibitors and ARBs.

Study patients

Japanese outpatients with mild to moderate CHF who met the following inclusion criteria were enrolled: age ≥ 20 years; previously treated with ACE inhibitors regardless of duration; considered unsuitable by the investigators for treatment with ACE inhibitors; and New York Heart Association (NYHA) functional class II–III. The main exclusion criteria included: unstable angina; serious ventricular arrhythmia; serious valvular stenosis; hypertrophic obstructive cardiomyopathy; acute myocardial infarction within 4 weeks before the start of treatment; cerebrovascular disease, coronary-artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) within 12 weeks before the start of treatment; CABG or PCI implemented or scheduled after the start of the study; cardiogenic shock or SBP < 80 mmHg; serious respiratory disease; renal artery stenosis; hyperkalemia; pregnant or nursing women or women suspected of being pregnant; or patients considered ineligible by the investigators.

The study was performed at 50 centers in Japan between June 2006 and July 2008 in accordance with the Declaration of Helsinki, the International Conference on Harmonization and the Harmonized Tripartite Guidelines on Good Clinical Practice (GCP), and was approved by the Institutional Review Board at each study site. All patients provided written informed consent.

Study protocol

NYHA functional class, vital signs, adverse events (AEs), and the medication adherence were examined every 4 weeks throughout the study period. Echocardiography, a resting 12-lead electrocardiogram (ECG), and other laboratory tests were performed and assessed every 12 weeks.

Study endpoints

The primary efficacy endpoints were the changes from baseline in plasma brain natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVDd), and NYHA functional class at the end of treatment, using last observation carried forward data analysis. Other efficacy measures included the changes from baseline in left ventricular end-systolic dimension (LVDs), 12-lead ECG findings, and body weight at the end of treatment. The following outcome measures were assessed: adverse drug reactions, cardiovascular events, death from cardiovascular events, hospitalization or death due to HF deterioration, nonfatal myocardial infarction, and addition or dose escalation of concomitant medications for HF (continuous oral medication over 2 weeks). Reasons for considering ACE inhibitor treatment inappropriate, and dose escalation/reduction or continuation of the same dose were also recorded.

Statistical analysis

To allow for possible withdrawals/discontinuations, we planned to enroll 300 patients in the clinical study. For the primary efficacy endpoints, the mean, standard deviation (SD), and the two-sided 95% confidence interval (CI) were calculated by applying a one-sample *t* test. The distributions of the data of changes in plasma BNP were highly skewed by outliers. Therefore, the geometric means and the two-sided 95% CIs were calculated by converting the means of log-transformed BNP values and the two-sided 95% CIs back to the original scale using back transformation for these indices. For these variables, a one-sample *t* test was performed by using log-transformed values. Eligible patients were divided into 2 groups based on the candesartan dose at the end of treatment: low-dose (LD, 2 or 4 mg) and high-dose (HD, 8 mg). To compare the 2 groups, analysis of covariance (ANCOVA) was performed using

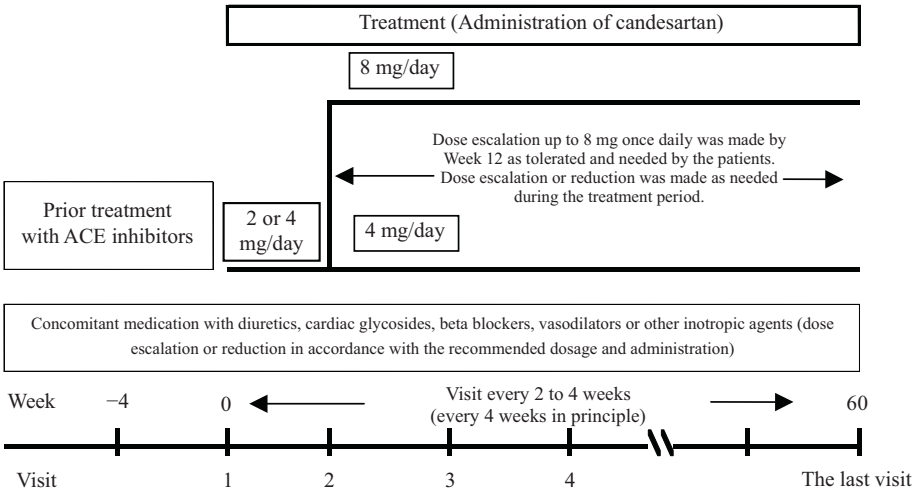

Fig. 1. Study design. ACE, angiotensin-converting enzyme.

LD and HD as independent variables and baseline values as covariates for the primary endpoints (dependent variables) except for the NYHA class for which Fisher's exact test was carried out. For the change from baseline of the log-transformed BNP and the change from baseline of LVEF and LVDd, ANCOVA was also performed using the dose at the end of treatment (LD or HD) as the independent variable, and baseline values as covariates. For the safety evaluation, SBP, diastolic blood pressure (DBP), pulse rate, estimated glomerular filtration rate (eGFR), and hemoglobin were analyzed as well. The efficacy endpoints were evaluated in the full analysis set (FAS) and the AEs were assessed in the safety analysis set (SAS). For all statistical analysis, the significance level was set at 0.05 (two-sided).

Results

Study patients

Out of 308 patients enrolled in this study, 19 were excluded due to a major violation of GCP and the remaining 289 were included in the FAS and SAS population. Of these 289 patients, 252 completed the study medication and 37 discontinued the medication due to AEs in 27 patients, major protocol deviation in 2 patients, spontaneous withdrawal in 2 patients, and other reasons in 6 patients. Most patients (98.6%) had medication adherence rates of at least 90%.

The demographic and baseline clinical characteristics are summarized in Table 1. Plasma BNP, LVEF, LVDd, and LVDs values at the baseline did not differ between the groups.

The most common reason for considering ACE inhibitor treatment inappropriate was "cough" [95.2% (275/289 patients)], followed by "decreased blood pressure" [0.7% (2/289 patients)].

The dose adjustment scheme during the treatment period is summarized in Table 2. The starting dose was 4 mg once daily in 70.9% of patients (205/289) and 2 mg once daily in 29.1% (84/289). The daily dose at the end of treatment was 8 mg in 58.8% of patients (170/289), 4 mg in 40.5% (117/289), and 2 mg in 0.7% (2/289).

Regarding dose adjustment, the most common reason for continuing the 4-mg dose was "dose escalation not needed because response is sufficient" (63.7%). Among the reasons for increasing the dose to 8 mg, "higher efficacy of the drug anticipated" (85.9%) was more common than "insufficient response" (12.4%). The most common reason for continuing the dose of 8 mg was "being well tolerated" (99.9%).

Table 1
Demographic and baseline clinical characteristics.

Item/category	Total	LD	HD	*p*-Value
No. of patients	289	119	170	
Age (years)				
33–64	102 (35.3)	47 (39.5)	55 (32.4)	
65–74	114 (39.4)	37 (31.1)	77 (45.3)	
75–89	73 (25.3)	35 (29.4)	38 (22.4)	
	67.5 ± 9.8	67.4 ± 10.7	67.5 ± 9.2	0.9389
Gender				
Male	187 (64.7)	79 (66.4)	108 (63.5)	0.6169
Female	102 (35.3)	40 (33.6)	62 (36.5)	
Height (cm)	159.6 ± 9.2	159.6 ± 8.8	159.7 ± 9.6	0.9776
Body weight (kg)	63.1 ± 12.7	62.2 ± 12.0	63.7 ± 13.2	0.3496
BMI (kg/m^2)	24.6 ± 3.8	24.3 ± 3.5	24.8 ± 4.0	0.2301
NYHA functional class				
Class I	0 (0.0)	0 (0.0)	0 (0.0)	
Class II$_S$	196 (67.8)	79 (66.4)	117 (68.8)	
Class II$_M$	66 (22.8)	31 (26.1)	35 (20.6)	0.4357
Class III	27 (9.3)	9 (7.6)	18 (10.6)	
Class IV	0 (0.0)	0 (0.0)	0 (0.0)	
Systolic blood pressure (mmHg)	129.1 ± 16.7	123.9 ± 14.8	132.7 ± 17.0	<0.0001
Diastolic blood pressure (mmHg)	73.4 ± 11.5	70.4 ± 9.8	75.6 ± 12.1	0.0001
Cardiothoracic ratio (%)	53.0 ± 6.2	52.6 ± 6.0	53.3 ± 6.3	0.3804
Brain natriuretic peptide (pg/mL)	125.5 ± 172.4	122.4 ± 183.7	127.7 ± 164.5	0.7957
Left ventricular end-diastolic dimension (mm)	51.7 ± 8.2	52.4 ± 9.1	51.2 ± 7.5	0.2295
Left ventricular end-systolic dimension (mm)	36.2 ± 10.1	37.1 ± 10.9	35.6 ± 9.6	0.236
Left ventricular ejection fraction (%)	56.8 ± 15.6	56.1 ± 14.7	57.2 ± 16.1	0.5397
Major cause of HF				
Dilated cardiomyopathy	52 (18.0)	23 (19.3)	29 (17.1)	
Ischemic heart disease	91 (31.5)	42 (35.3)	49 (28.8)	
Hypertensive heart disease	60 (20.8)	12 (10.1)	48 (28.2)	0.0063
Valvular disease	57 (19.7)	28 (23.5)	29 (17.1)	
Other	29 (10.0)	14 (11.8)	15 (8.8)	
Duration of HF (years)	4.9 ± 4.1	5.9 ± 4.5	4.2 ± 3.6	0.0005
ACE inhibitors/ARBs discontinued within 12 weeks before the start of the treatment period	154 (53.3)	56 (47.1)	98 (57.6)	0.0758
Concomitant medications for HF at the beginning of treatment[a]				
Overall	208 (72.0)	91 (76.5)	117 (68.8)	0.1543
Diuretic	149 (51.6)	77 (64.7)	72 (42.4)	0.0002
Beta blocker	102 (35.3)	43 (36.1)	59 (34.7)	0.8025
Digoxin/digitoxin	88 (30.4)	37 (31.1)	51 (30.0)	0.8426
Vasodilator	19 (6.6)	8 (6.7)	11 (6.5)	0.9322
Other	13 (4.5)	8 (6.7)	5 (2.9)	0.1269

BMI, body mass index; NYHA, New York Heart Association; HF, heart failure; LD, low-dose group (2 or 4 mg once daily); HD, high-dose group (8 mg once daily); ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker. Values are presented as *n* (%) or mean ± SD.

[a] One patient may have 2 or more concomitant medications.

Table 2
Dose adjustment scheme during the treatment period.

Item/category	Total *n* (%)
No. of patients	289
Dose adjustment	
2 mg once daily	2 (0.7)
2 → 4 mg once daily	42 (14.5)
2 → 4 → 8 mg once daily	37 (12.8)
2 → 4 → 8 → 4 mg once daily	3 (1.0)
4 mg once daily	68 (23.5)
4 → 8 mg once daily	133 (46.0)
4 → 8 → 4 mg once daily	4 (1.4)
Starting dose	
2 mg once daily	84 (29.1)
4 mg once daily	205 (70.9)
Dose at the end of treatment	
2 mg once daily	2 (0.7)
4 mg once daily	117 (40.5)
8 mg once daily	170 (58.8)

Values represent number (%) of patients.

Efficacy

The geometric mean of BNP significantly declined from 60.9 pg/mL to 55.3 pg/mL at week 24 and remained at a low level through to week 60 (49.5 pg/mL). At the end of treatment, the geometric mean of BNP was 53.2 pg/mL and the ratio to the baseline value was 0.87 [two-sided 95% CI (0.798 to 0.955)], indicating a significant BNP reduction from the baseline ($p = 0.0030$). With ANCOVA, using the final dose as factor and the baseline value as covariate, the regression coefficients of BNP to the effect of the baseline values were significant negative values. In terms of BNP changes, the higher the baseline level, the greater was the BNP reduction observed: each ratio to baseline value was 0.86 in $20 \leq$ BNP < 100 pg/mL ($n = 127$), 0.77 in $100 \leq$ BNP < 200 pg/mL ($n = 49$), and 0.71 in BNP ≥ 200 pg/mL ($n = 56$). No positive relationship was found between the reduction of BNP and patient age or gender.

The time course of BNP changes in the LD and HD groups is shown in Fig. 2. The geometric mean BNP levels in the HD group significantly declined from 61.6 pg/mL at baseline to 54.7 pg/mL at week 24 and remained at a low level up to week 60 (46.2 pg/mL), whereas no significant changes occurred in the LD group. At the end of treatment, the geometric mean BNP value was 50.1 pg/mL and the ratio to the baseline value was 0.81 in the HD group [95% CI (0.726 to 0.912)] ($p = 0.0005$). Plasma BNP at the end of treatment also tended to be lower in the HD group than in the LD group, but did not reach statistical significance ($p = 0.0527$).

Mean LVEF significantly increased from 56.8% at the baseline to 58.2% at week 12 and remained at a similar level until week 60. At the end of treatment, mean LVEF was 58.4% and the mean value of individual percent change from the baseline was 6.8% [95% CI (2.97 to 10.56)] ($p = 0.0005$). With ANCOVA, using the final dose as factor and the baseline value as covariate, the regression coefficients of LVEF to the effect of the baseline values were significant negative values. In terms of LVEF changes, the lower the baseline level, the higher was the improved rate obtained: the percent change from the baseline was 37.5% in LVEF $< 40.0\%$ ($n = 45$), 5.3% in $40 \leq$ LVEF $< 55\%$ ($n = 70$), and -0.7% in LVEF $\geq 55\%$ ($n = 172$). No positive relationship was found between LVEF increase and patient age or gender.

The time course of LVEF changes in the LD and HD groups is shown in Fig. 3. In the LD group, no significant LVEF changes were found throughout the treatment period and the mean value of individual percent change from the baseline was 2.0% [95% CI (-2.63 to 6.59)] at the end of treatment. In the HD group, the mean LVEF significantly increased from 57.2% at the baseline to 59.3% at week 12, reached the maximal value (60.8%) at week 48, and remained at a high level through to week 60 (60.7%). At the end of treatment, the mean LVEF was 60.1% and the mean value of individual percent change from the baseline was 10.1% [95% CI (4.51 to 15.61)] ($p = 0.0005$). A significant difference in the percent changes from the baseline in LVEF [9.0%, 95% CI (2.26 to 15.83)] was found between the LD and HD groups at the end of treatment ($p = 0.0092$), indicating a dose–response relationship.

The time course of LVDd changes in the LD and HD groups is shown in Fig. 3. Changes from the baseline in LVDd were minimal throughout the treatment period. At the end of treatment, the mean LVDd was 52.0 mm (mean percent change from baseline, -0.2%) in the LD group and 50.1 mm (mean percent change from baseline, -1.7%) in the HD group. There were no significant differences in the percent changes from the baseline LVDd values [-2.0%, 95% CI (-4.65 to 0.64)] between the LD and HD groups.

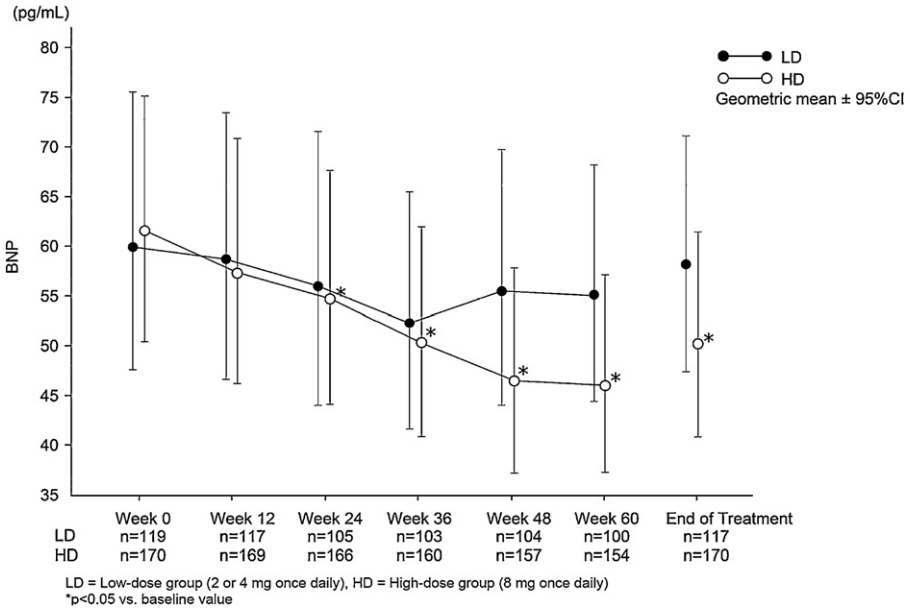

Fig. 2. Time course of plasma brain natriuretic peptide (BNP) levels in the low-dose (LD) and high-dose (HD) groups.

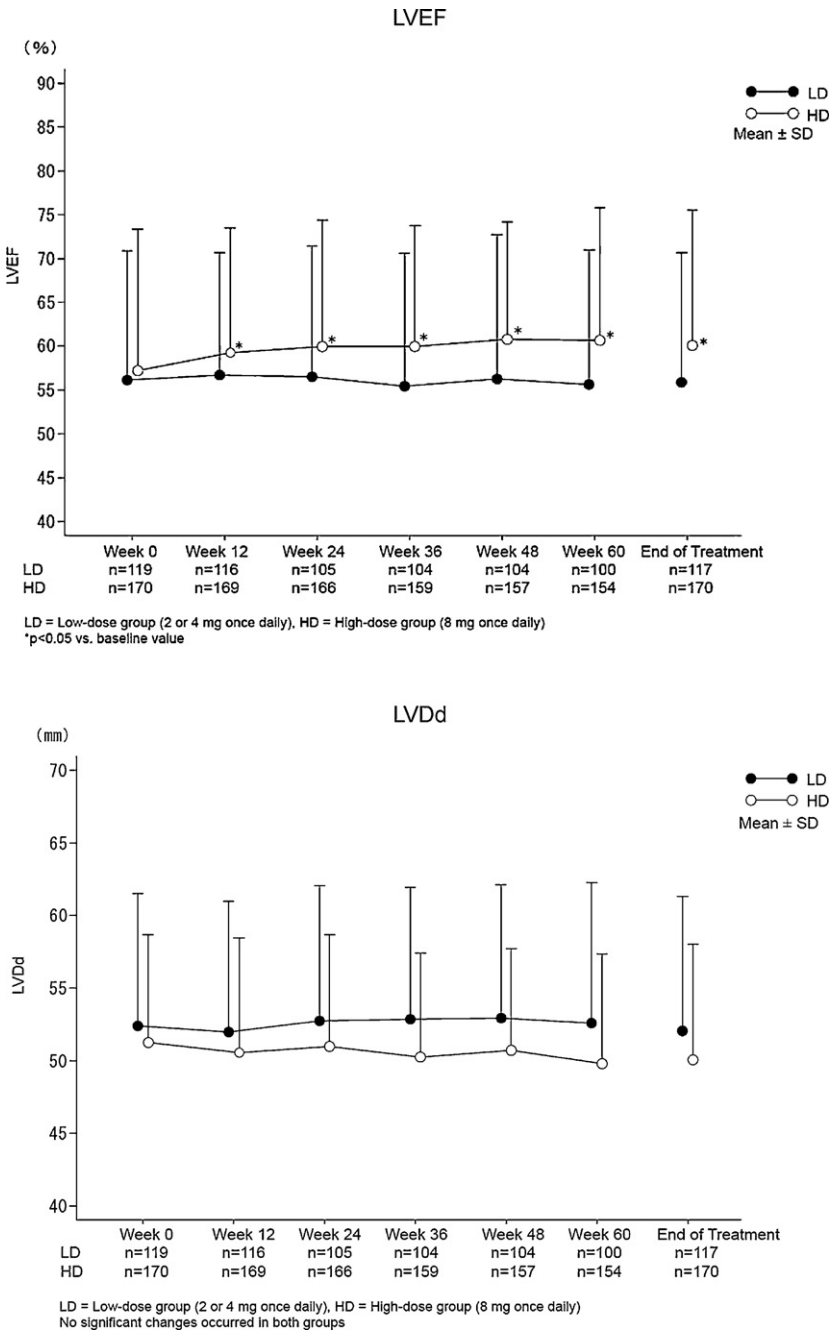

Fig. 3. Time course of echocardiography parameters in LD and HD groups. LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic dimension; LD, low dose; HD, high dose.

Of the 119 patients in the LD group, 79 were in NYHA functional class II_S, 31 in II_M, and 9 in III at baseline (Fig. 4). NYHA functional class progressively improved after the start of treatment and showed the maximal improvement in 23.8% of patients (24/101) at week 56. At the end of treatment, 21.2% of patients (25/118) showed an improvement, but 76.3% (90/118) were without change. Deterioration occurred in 2.5% of patients (3/118).

Of the 170 patients in the HD group, 117 were in class II_S, 35 in II_M, and 18 in III at baseline (Fig. 4). The improved rate increased soon after the start of treatment and reached the maximal value, improvement in 20.8% of patients (32/154) at week 60. At the end of treatment, 20.6% of patients (35/170) exhibited an improvement, but 79.4% (135/170) were without change. No patients experienced deterioration of NYHA functional class. With the Wilcoxon signed rank test, significant differences were found between the changes in NYHA functional class in patients before and after the treatment in both the HD and the LD groups ($p < 0.001$).

HF-associated events occurred in 18.3% of study patients (53/289), 19.3% (23/119) in the LD group, and 17.6% (30/170) in the HD group (Table 3). The incidences of HF-associated events did not differ between the LD and HD groups.

Safety

A total of 1059 treatment-emergent AEs were reported in 92.4% of patients (267/289). There were 65 serious AEs reported in 17.0% of patients (49/289), which included 3 deaths (3/289, 1.0% of patients). Among the serious AEs, 4 drug-related AEs occurred in

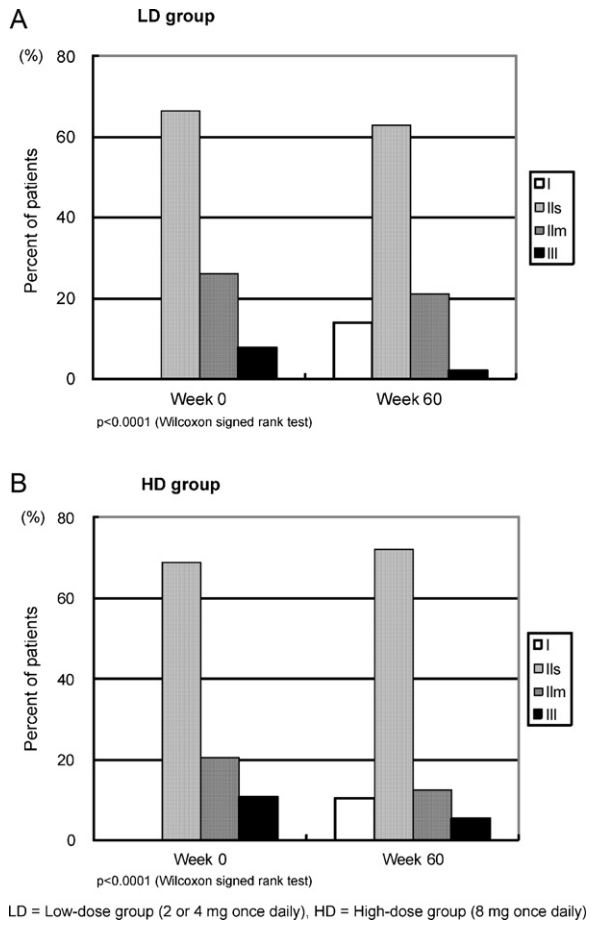

Fig. 4. Changes in New York Heart Association functional class in the low-dose (LD) and high-dose (HD) groups.

1.4% (4/289), including acute pyelonephritis, cerebral hemorrhage, vertigo, and angina pectoris (1 event each). Drug-related AEs leading to discontinuation occurred in 3.8% of patients (11/289).

The incidence of drug-related AEs was slightly higher in the LD [23.5% (28/119 patients)] than in the HD [17.1% (29/170 patients)] group, but no significant differences in severity or class of drug-related events were found between groups.

No clinically significant abnormalities were observed in the vital signs and clinical laboratory test results. Mean values (SD) of SBP, DBP, pulse rate, eGFR, and hemoglobin at baseline and at the end of treatment are shown in Table 4. The adjusted mean SBP change in the LD group had a statistically significant larger value than that in the HD group [−8.2 mmHg in the LD group and −1.3 mmHg in the HD group ($p = 0.0003$)]. There were no other significant differences in the other parameters.

Table 4
Vital signs, eGFR, and hemoglobin at baseline and at the end of treatment in LD and HD groups.

	Week 0 Mean ± SD	End of treatment Mean ± SD	p-Value*
Systolic BP (mmHg)			
LD	123.9 ± 14.8	118.7 ± 15.9	0.0003
HD	132.7 ± 17.0	129.6 ± 17.6	
Diastolic BP (mmHg)			
LD	70.4 ± 9.8	68.4 ± 11.2	0.0556
HD	75.6 ± 12.1	73.1 ± 12.5	
Pulse rate[a] (beats/min)			
LD	72.8 ± 10.3	74.0 ± 10.1	0.0686
HD	72.8 ± 11.9	71.8 ± 12.1	
eGFR (mL/min/1.73 m^2)			
LD	65.3 ± 17.5	64.7 ± 17.9	0.2008
HD	63.5 ± 18.3	62.1 ± 18.1	
Hemoglobin (g/dL)			
LD	13.6 ± 1.6	13.2 ± 1.7	0.9143
HD	13.6 ± 1.8	13.2 ± 1.9	

BP, blood pressure; eGFR, estimated glomerular filtration rate; LD, low-dose group (2 or 4 mg once daily); HD, high-dose group (8 mg once daily).

[a] Pulse rates of patients with atrial fibrillation were also included in these results.

* p-Values were calculated by ANCOVA using baseline value as covariates and the final dose as an independent variable.

Overall, a 60-week treatment with recommended candesartan doses was well tolerated in patients with mild to moderate CHF.

Discussion

This study was designed to closely represent the clinical use of recommended doses of candesartan. In most patients, the dose was increased from 4 mg to 8 mg at a time point between week 4 and week 12, in anticipation of a higher efficacy of candesartan. Long-term treatment with candesartan resulted in significant changes from the baseline in plasma BNP levels and LVEF as well as an improvement in NYHA functional class. The improvements in BNP levels and LVEF were significantly greater in the HD than in the LD group, while NYHA functional class improved in approximately 20% of patients in both groups.

In the ARCH-J study in Japanese patients with congestive HF, 6-month treatment with candesartan 8 mg once daily significantly reduced the progression of congestive HF compared with the placebo (7.4% vs. 22.2%) and the development of cardiovascular events (10.8% vs. 22.9%) [6].

Mean baseline LVEF values were 56.1% in the LD and 57.2% in the HD groups in this study and these values were higher than that (35.3%) in the candesartan group in the ARCH-J study. The proportion of patients with more preserved LVEF was higher in this study than in the ARCH-J study suggesting that these patients were

Table 3
HF-associated events in total patients of LD and HD groups.

HF-associated events	Total (N = 289)	LD (N = 119)	HD (N = 170)	p-Value
Any of the overall events	53 (18.3)	23 (19.3)	30 (17.6)	0.528
Either hospitalization for HF deterioration, or addition or dose escalation of concomitant medications for HF[a]	44 (15.2)	19 (16.0)	25 (14.7)	0.6165
Cardiovascular events	21 (7.3)	8 (6.7)	13 (7.6)	0.9132
Death from cardiovascular events	1 (0.3)	1 (0.8)	0 (0.0)	0.2193
Hospitalization for HF deterioration	7 (2.4)	3 (2.5)	4 (2.4)	0.855
Hospitalization for or death from HF deterioration	7 (2.4)	3 (2.5)	4 (2.4)	0.855
Nonfatal myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	–
Addition or dose escalation of concomitant medications for HF[a]	41 (14.2)	17 (14.3)	24 (14.1)	0.7792

HF, heart failure; LD, low-dose group (2 or 4 mg once daily); HD, high-dose group (8 mg once daily). Values represent number (%) of patients who had HF-associated events. No significant differences in the incidences of HF-associated events were found between the LD and HD groups with the log-rank test.

[a] Continuous oral medication over 2 weeks.

considered to be at relatively low risk for cardiovascular mortality [3,7,8]. In the present study, in terms of LVEF changes, the lower the baseline level, the higher the improved rate obtained. The LVEF change from 57.2% at the baseline to 60.7% at week 60 in the HD group was less than that (from 35.1% to 40.9%) with 6-month candesartan treatment in the ARCH-J study. This lower degree of improvement in LVEF might be due to the high baseline LVEF levels in the present study and the differences in the underlying diseases of HF, complications such as hypertension and diabetes, treatment duration, and concomitant medications between these 2 studies. The underlying diseases of HF in the candesartan group in the ARCH-J study were dilated cardiomyopathy (55.4%), myocardial infarction (23.0%), hypertension (7.4%), and valvular disease (4.1%).

As is well known, plasma BNP was reported to be an important predictor of mortality and first morbid event in CHF [9]. Mean baseline BNP levels, 122.4 pg/mL (median, 64.0 pg/mL) in the LD and 127.7 pg/mL (median, 74.1 pg/mL) in the HD groups, in this study were lower than the 181 pg/mL (median, 97 pg/mL) reported in patients enrolled in the Valsartan Heart Failure Trial (Val-HeFT) [10]. In the present study, a higher baseline BNP level was associated with a greater reduction due to treatment with candesartan. Similar effects were also reported in the Val-HeFT [10]. These findings suggest that a significant BNP-reducing effect was not obtained specifically with the LD treatment possibly because of the low baseline BNP levels in the present study population.

The overall incidences of HF-associated events were 19.3% in the LD and 17.6% in the HD groups; the addition/dose increase of HF medication (14.3% in the LD and 14.1% in the HD group), cardiovascular events (6.7% in the LD and 7.6% in the HD group), and hospitalization or death due to worsening HF (2.5% in the LD and 2.4% in the HD group). These results were comparable with a specified drug-use results survey of candesartan in 1087 Japanese CHF patients, in which cardiovascular events and hospitalization or death due to HF occurred in 2.9% and 6.0% of patients, respectively, during a 1-year observation period (from the data attached to the reexamination applications). The incidence of the addition/increase of HF medication in this study was higher than that in the ARCH-J study (2.0%) and those of cardiovascular events and hospitalization for HF were lower (10.8% and 5.4%, respectively). These differences might be attributable to the high baseline LVEF levels in the present study patients and the differences in the underlying diseases of HF, complications, and treatment conditions between these 2 studies.

Previous large-scale clinical trials of candesartan, valsartan, and losartan for CHF demonstrated that significant reductions in cardiovascular mortality and morbidity were produced by high-dose ARBs titrated as tolerated to the target doses [11–14]. In the treatment with candesartan for patients with symptomatic HF, high-dose treatment titrated as tolerated to a target dose of 32 mg once daily (mean daily dose of 24 mg) reduced cardiovascular death and hospitalization for HF [11,12]. These studies indicate that the highest possible dose of candesartan tolerated by patients is preferable. The present results are also considered to be in agreement with these studies.

Study limitations

This study has a couple of limitations. Firstly, this was not a randomized double-blinded study, and therefore the decision about dose titration of candesartan was delegated to each physician. Thus, the dose may have been affected by the patient background and status: lower SBP in the LD group might have caused hesitation to titrate the dose further. Secondly, the population enrolled in this study showed CHF of relatively mild severity. Consequently, the degree of improvement was relatively small, especially in the LD group. However, despite these limitations, this study reflects the clinical practice in the real-world of CHF treatment in Japan showing the effects of candesartan within the range of approved doses.

Conclusions

A 60-week treatment with the recommended regimen significantly improved plasma BNP levels, LVEF, and NYHA functional class and candesartan was well tolerated in Japanese patients with mild to moderate CHF. Improvements in plasma BNP levels and LVEF were significantly greater with the higher dose of candesartan treatment.

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