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ORIGINAL ARTICLE

Nifedipine controlled-release 40 mg b.i.d. in Japanese patients with essential hypertension who responded insufficiently to nifedipine controlled-release 40 mg q.d.: a phase III, randomized, double-blind and parallel-group study

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This phase III, multicenter, randomized, double-blind, parallel-group study compared the efficacy and safety of nifedipine controlled-release (CR) 40 mg twice daily (b.i.d.) and once daily (q.d.) in 325 Japanese patients with essential hypertension uncontrolled with nifedipine CR 40 mg q.d. (ClinicalTrials.gov record: NCT01287260). The primary endpoint was the change from baseline in trough seated diastolic blood pressure (DBP) after 8 weeks. Nifedipine CR 40 mg b.i.d. showed significantly greater reductions in trough seated DBP (-7.7 ± 0.6 mm Hg *vs.* -3.6 ± 0.6 mm Hg) and trough seated systolic blood pressure (BP) (-11.1 ± 0.9 mm Hg *vs.* -3.7 ± 0.9 mm Hg) after 8 weeks of treatment compared with nifedipine CR 40 mg q.d. (both $P<0.0001$). At week 8, BP target achievement and responder rates were higher with nifedipine CR 40 mg b.i.d. (21.5% and 42.4% *vs.* 10.3% and 19.5%, respectively). Adverse events considered related to the study drug were reported in 9.0 and 9.7% of patients receiving nifedipine CR 40 mg b.i.d. and q.d., respectively. The frequency of drug-related adverse events commonly reported with nifedipine CR (headache, hot flush, palpitations, peripheral edema, hypotension, dizziness, tachycardia) was low and the results were similar between the treatment groups. In conclusion, a higher dose of nifedipine CR was associated with greater efficacy and a safety profile similar to that of the currently approved dose (40 mg q.d.) in Japanese patients with essential hypertension, and it may offer a valuable treatment choice for patients who do not achieve target BP levels with standard treatment.
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Keywords: controlled-release; hypertension; monotherapy; nifedipine 80 mg per day; phase III

INTRODUCTION

The impact of essential hypertension on population mortality and morbidity has been widely recognized.[1] Hypertension is one of the leading causes of cardiovascular disease; compared with normotensive patients, individuals with hypertension have almost twice the risk of developing coronary artery disease and a much higher risk of stroke.[2]

The fundamental goal of the treatment of hypertension is to reduce the risk of cardiovascular morbidity and mortality, and this attitude is reflected in most major treatment guidelines.[2–5] In Japan, the Japanese Society of Hypertension 2009 treatment guidelines for the management of hypertension (JSH 2009 guidelines)[3] propose that blood pressure (BP) should be strictly controlled with recommended target BP levels of $<130/85$ mm Hg in young or middle-aged patients and $<140/90$ mm Hg in elderly patients. Furthermore, in high-risk patients (such as those with diabetes mellitus (DM), chronic kidney disease (CKD) or those who have experienced myocardial infarction

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(MI)) the JSH 2009 guidelines recommend that BP should be lowered to $<130/80$ mm Hg as quickly as possible to prevent the occurrence of cardiovascular events.[3] However, the rate of achievement of target BP levels in current clinical practice is low: findings from the Japan Home versus Office blood pressure Measurement Evaluation study indicated that ~60% of patients did not meet the target BP levels described in the guidelines.[6] This was also demonstrated in other surveys, which showed that the achievement of target BP goals was low, particularly in patients with comorbid conditions such as DM or renal disease.[7,8]

To treat hypertension, the JSH 2009 guidelines recommend the use of calcium-channel blockers (CCBs), angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, β-adrenoceptor antagonists and diuretics, either alone or in combination as induction and maintenance treatments.[3] Nifedipine is a dihydropyridine CCB that was initially developed for the prophylaxis of angina symptoms but is now widely used as an antihypertensive agent.[9] The original immediate-release capsule formulation of nifedipine was developed over 30 years ago and required administration three times a day.[10] Subsequently, nifedipine retard tablet, which is a slow-release formulation (Adalat L; Bayer Yakuhin Ltd., Osaka, Japan), and an advanced controlled-release (CR) formulation of nifedipine (Adalat CR; Bayer Yakuhin Ltd.) have been developed. The CR formulation, which consists of a coat-core tablet and a hydrophilic matrix, was reviewed previously.[11] This formulation retains the antihypertensive effect of nifedipine while reducing side effects and improving compliance.[12–14] It has been approved in Japan at the maximum dose of 40 mg per day for hypertensive patients; however, increasing the maximum dose of nifedipine to 80 mg per day may improve treatment outcomes in those patients who do not achieve target BP levels. A recent phase II study, which was a randomized, double-blind, crossover study, compared the efficacy and safety of nifedipine CR, administered at a dose of 40 mg (once daily (q.d.)) or 80 mg (40 mg twice daily (b.i.d.) or 80 mg q.d.) in patients with essential hypertension whose BP was not sufficiently controlled with nifedipine CR 40 mg OD.[15] That study demonstrated that nifedipine CR 40 mg b.i.d. improved treatment outcomes. It also highlighted that the best treatment regimen for high-dose nifedipine CR was 40 mg b.i.d. as the plasma concentrations of nifedipine were higher at trough (assessed 24 h after the morning dose). In contrast, although nifedipine CR at 80 mg q.d. was associated with a similar efficacy to nifedipine CR 40 mg b.i.d., the trough plasma levels of nifedipine CR in patients receiving 80 mg q.d. were similar to those observed in the nifedipine 40 mg q.d. treatment group.[15]

The objective of the present study was to further demonstrate the superior efficacy of nifedipine CR 40 mg b.i.d. *vs.* 40 mg q.d. in Japanese patients with essential hypertension who did not achieve target BP with nifedipine CR 40 mg q.d., and to assess the safety and tolerability of the 40 mg b.i.d. dose regimen.

METHODS

Study design

This was a phase III, multicenter, randomized, double-blind, parallel-group study, which compared the efficacy and safety of nifedipine CR 40 mg b.i.d. and nifedipine CR 40 mg q.d. in Japanese patients aged $\geqslant 20$ years with essential hypertension who were not sufficiently controlled with nifedipine CR 40 mg q.d. (ClinicalTrials.gov record: NCT01287260). This study was conducted in 21 sites across Japan and consisted of a 4-week screening period and an 8-week treatment period. During the 4-week screening period, nifedipine CR 40 mg was administered q.d. in a single-blind fashion. At visit 3 (week 0; baseline), patients were randomized to receive nifedipine CR 40 mg b.i.d. or nifedipine CR 40 mg q.d. during the double-blind treatment period (Figure 1).

Patients were enrolled into the baseline screening period if their seated diastolic BP (DBP) was $\geqslant 90$ mm Hg despite more than 4 weeks of treatment with antihypertensives. Patients could continue into the double-blind treatment period if they had not achieved target DBP levels after receiving 4 weeks of treatment with nifedipine CR 40 mg q.d. during the screening period. This target was designated as follows: $\geqslant 90$ mm Hg in elderly patients without DM, CKD or prior myocardial infarction (pMI); $\geqslant 85$ mm Hg in non-elderly patients without DM, CKD or pMI; $\geqslant 80$ mm Hg in patients with DM, CKD or pMI. Patients were also required to have an absolute difference of <10 mm Hg in their seated DBP between visit 2 (week −2) and visit 3 (week 0).

Patients were excluded from the study if they had a seated DBP $\geqslant 110$ mm Hg or a systolic BP (SBP) $\geqslant 180$ mm Hg, secondary hypertension or hypertensive emergency, a history of cardiovascular, cerebrovascular ischemic events, intracranial or subarachnoid hemorrhage in the 6 months before study entry, congestive heart failure, severe hematopoietic dysfunction or a malignant tumor, or aortic stenosis, mitral stenosis, pulmonary hypertension or cardiogenic shock. Other exclusion criteria were generally consistent with the absolute and relative contraindications and precautions for antihypertensive use.

The protocol was reviewed and approved by each study site's Independent Ethics Committee or Institutional Review Board before the start of the study. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP). Written informed consent for enrollment in the study was obtained from all patients or their legally acceptable representative.

Treatment outcomes

The primary efficacy endpoint was the change from baseline in trough seated DBP at the end of the double-blind treatment period (8 weeks). Secondary and other efficacy endpoints were as follows:

Secondary endpoints

1. The change from baseline to 8 weeks in seated SBP
2. Patient achievement rates, defined as the proportion of patients achieving BP targets according to the JSH 2009 guidelines[3]
3. Patient responder rates, defined as the proportion of patients achieving BP targets according to the JSH 2009 guidelines or a >10 mm Hg reduction of DBP from baseline

Other endpoint

1. Blood pressure and pulse rate at each visit

Achievement and responder rates were assessed at the end of the double-blind treatment period (8 weeks). BP and pulse rate were recorded at each study visit. Patients were instructed to visit the hospital without taking medication on the morning of each visit. BP was measured using a mercury sphygmomanometer or a validated electronic device. Before recording the BP, patients were required to rest in a sitting position for at least 5 min. Two stable readings (<5 mm Hg difference) at 1- or 2-min intervals were averaged. If the difference between the two readings was 5 mm Hg or more, additional readings were obtained and two stable readings were averaged.

Drug-related adverse events that occurred during the double-blind treatment period were recorded, and their severity and relationship to the study drug were determined by the investigator. Other safety assessments included 12-lead ECG and laboratory tests to measure hematology, clinical chemistry and urinalysis parameters.

Statistical analysis

The primary efficacy outcome was the change from baseline at 8 weeks in trough seated DBP. The two-sided *t*-test was performed by using an analysis of covariance model with the baseline value as a covariate and term for treatment group as a fixed effect. Based on the analysis of covariance model, the least-squares mean (LSM) difference in the change from baseline between treatment

groups and 95% confidence interval (CI) were also estimated. Assuming a common standard deviation of 7.5 mm Hg, a power of 95% and a two-sided significance level of 5%, 164 patients per treatment group were required to detect a difference of 3.0 mm Hg. Assuming a 20% screening failure during the screening period and ~5% dropout after randomization, 434 enrolled patients and 346 randomized patients were required.

Evaluation of all efficacy variables was based on the full analysis set, defined as all patients who received at least one dose of the study medication during the double-blind treatment period and had at least one observation recorded following treatment commencement. Evaluation of all safety variables was based on the safety analysis set (SAS), which was defined as all patients who received at least one dose of the study medication during the double-blind treatment period. All statistical analyses for this study were performed using the software package SAS release 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Of the 430 patients who received nifedipine CR 40 mg q.d. during the single-blind screening period, 352 patients met the inclusion criteria and were randomized in the double-blind treatment period (Figure 2). Of the 352 patients in the SAS, one patient who was randomized to nifedipine CR 40 mg q.d. was excluded from the full analysis set as they had no efficacy data in the double-blind period. As 20 patients discontinued treatment, a total of 332 patients completed

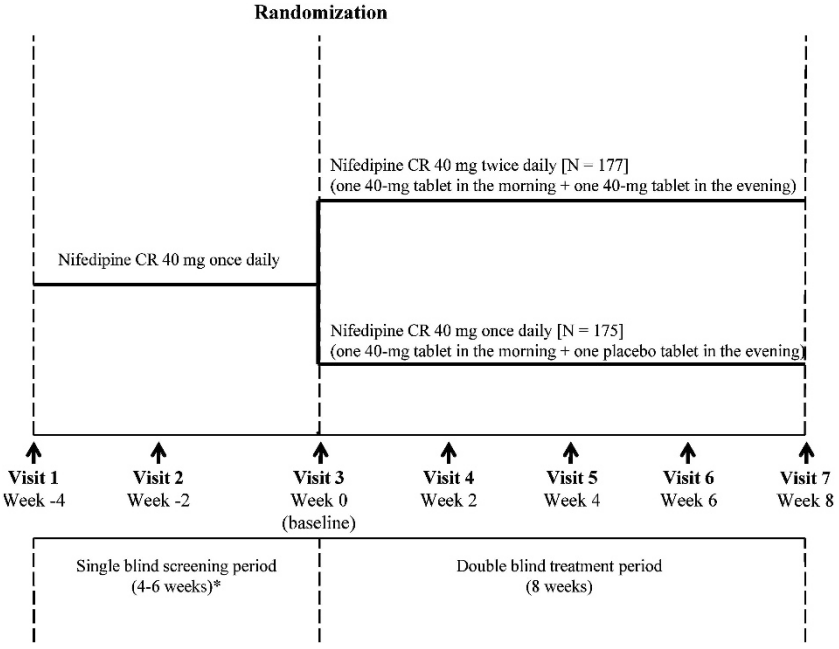

Figure 1 Study design. *When the difference in the patients' seated diastolic blood pressure between week −2 and week 0 was ⩾10 mm Hg, the baseline single-blind screening period was extended up to 6 weeks.

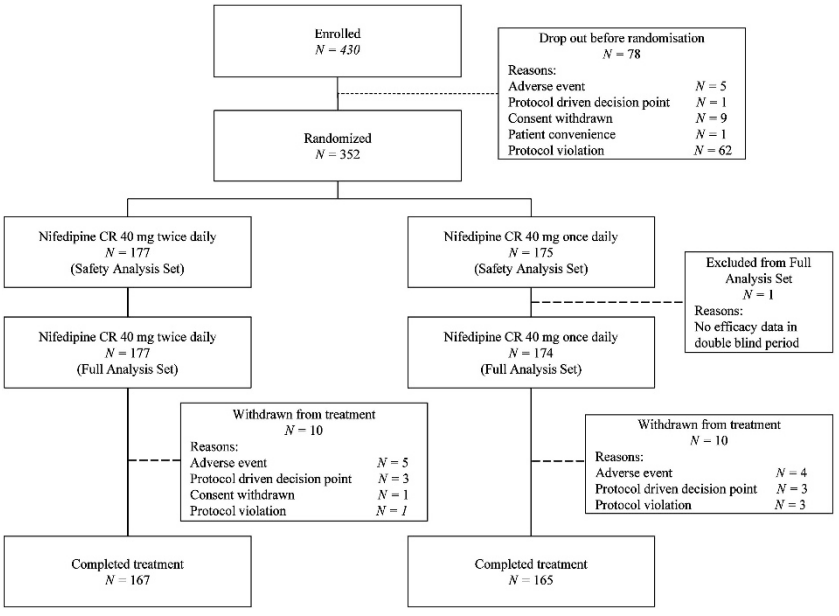

Figure 2 Flow chart of the patient randomization.

the double-blind treatment period. The reasons for treatment discontinuation included adverse events ($N=9$), protocol-driven decision point (such as the patient meeting exclusion criteria or requiring excluded concomitant medication; $N=6$), protocol violation ($N=4$) and consent withdrawal ($N=1$).

There were no meaningful differences between the two treatment groups with respect to demographic or baseline characteristics (Table 1). Patients had a mean age of 54.8 ± 10.1 years (range 29–85 years) and 74.4% were male. They had a mean DBP of 95.5 ± 6.1 mm Hg, a mean SBP of 147.5 ± 11.6 mm Hg, a mean bodyweight of 71.5 ± 14.0 kg and a mean body mass index of 26.0 ± 3.9 kg m^{-2}.

Efficacy

Primary endpoint. In the full analysis set, the LSM changes from baseline to week 8 in the primary endpoint trough seated DBP were −7.7 ± 0.6 mm Hg and −3.6 ± 0.6 mm Hg in the nifedipine CR 40 mg b.i.d. and 40 mg q.d. treatment groups, respectively. A statistically significant difference ($P<0.0001$) between the two treatment groups was observed at 8 weeks, with a LSM between-group difference of −4.1 mm Hg (95% CI: −5.7, −2.4) in favor of nifedipine CR 40 mg b.i.d. The difference between treatment groups was observed as early as 2 weeks into treatment and was maintained over the 8-week double-blind treatment period (Figure 3a).

Secondary and other endpoints. The LSM change from baseline in trough seated SBP at the end of the double-blind treatment period was −11.1 ± 0.9 mm Hg with nifedipine CR 40 mg b.i.d. compared with −3.7 ± 0.9 mm Hg with nifedipine CR 40 mg q.d., resulting in a statistically significant LSM between-group difference of −7.3 mm Hg (95% CI: −9.7, −4.9; $P<0.0001$) in favor of nifedipine CR 40 mg b.i.d. This greater reduction in SBP in nifedipine CR 40 mg b.i.d. was seen as early as week 2 and the mean SBP was maintained below 140 mm Hg (137.1–139.7 mm Hg) during the double-blind treatment period. In contrast, SBP levels in patients receiving nifedipine CR 40 mg q.d. remained above 140 mm Hg (142.3–144.8 mm Hg) during the double-blind treatment period (Figure 3b).

Compared with nifedipine CR 40 mg q.d. recipients, approximately twice the number of patients receiving nifedipine CR 40 mg b.i.d. achieved the target BP, with a treatment difference of 10.9% (95% CI: 3.5, 18.3) observed (Table 2). Similarly, the number of patients considered responders to nifedipine CR 40 mg b.i.d. was approximately twice the number of patients considered responders to nifedipine CR 40 mg q.d. (between-group difference 22.6%, 95% CI: 13.3, 32.0; Table 2). When analyzed by age and medical status, higher achievement and responder rates were observed with nifedipine CR 40 mg b.i.d. in both elderly and non-elderly patients who had no DM, CKD or pMI, compared with nifedipine CR 40 mg q.d. (Table 2). However, although patients with DM, CKD or pMI receiving nifedipine CR 40 mg b.i.d. had higher responder rates than patients receiving nifedipine CR 40 mg q.d., the achievement rates of those patients were low in both treatment groups (Table 2). Again, like the other variables evaluated, the differences between treatment groups in both BP target achievement and responder rates were seen as early as week 2.

The mean changes in pulse rate over the double-blind treatment period were small and no clinically significant difference in pulse rate between the treatment groups was observed (Figure 3c). The mean pulse rate in patients receiving nifedipine CR 40 mg b.i.d. was somewhat elevated in the double-blind treatment period compared

Table 1 Baseline characteristics and demographics in the safety analysis set

	Nifedipine CR 40 mg b.i.d. (N = *177*)	*Nifedipine CR 40 mg q.d.* (N = *175*)	*Total* (N = *352*)
Age, years			
Mean ± s.d.	55.3 ± 10.2	54.2 ± 10.1	54.7 ± 10.1
Range	33–85	29–82	29–85
Age group, n (%)			
<65 years	143 (80.8)	150 (85.7)	293 (83.2)
⩾65 years	34 (19.2)	25 (14.3)	59 (16.8)
Sex, n (%)			
Male	125 (70.6)	137 (78.3)	262 (74.4)
Female	52 (29.4)	38 (21.7)	90 (25.6)
Bodyweight, kg			
Mean ± s.d.	70.3 ± 12.6	72.6 ± 15.1	71.5 ± 14.0
Range	42.0–120.4	41.6–133.9	41.6–133.9
Body mass index, kg m^{-2}			
Mean ± s.d.	25.8 ± 3.5	26.2 ± 4.3	26.0 ± 3.9
Range	17.9–36.9	14.1–50.1	14.1–50.1
Duration of hypertension, years			
Mean ± s.d.	7.7 ± 7.5	6.6 ± 6.1	7.1 ± 6.9
Range	0.1–43.2	0.1–30.2	0.1–43.2
DBP, mm Hg			
Mean ± s.d.	95.3 ± 6.1	95.6 ± 6.2	95.5 ± 6.1
Range	83–109	85–109	83–109
SBP, mm Hg			
Mean ± s.d.	148.7 ± 11.4	146.4 ± 11.7	147.5 ± 11.6
Range	125–178	117–178	117–178
Pulse rate (beats min^{-1})[a]			
Mean ± s.d.	75.8 ± 9.6	75.7 ± 10.8	
Range	53–98	52–117	
Comorbid conditions, n (%)			
DM	20 (11.3)	16 (9.1)	36 (10.2)
CKD	8 (4.5)	4 (2.3)	12 (3.4)
pMI	1 (0.6)	1 (0.6)	2 (0.6)
Previous hypertension therapy, n (%)			
Calcium-channel blockers	149 (84.2)	148 (84.6)	297 (84.4)
RAS agents	70 (39.5)	62 (35.4)	132 (37.5)
β-blockers	6 (3.4)	5 (2.9)	11 (3.1)
Antihypertensives	5 (2.8)	1 (0.6)	6 (1.7)
Diuretics	3 (1.7)	3 (1.7)	6 (1.7)
Serum lipid reducing agents	2 (1.1)	3 (1.7)	5 (1.4)
Urologicals	4 (2.3)	1 (0.6)	5 (1.4)
Smoking status, n (%)			
Non-smoker	83 (46.9)	75 (42.9)	158 (44.9)
Previous or present smoker	94 (53.1)	100 (57.1)	194 (55.1)

Abbreviations: b.i.d., twice daily; CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellitus; *n*, number of patients; *N*, total number of patients evaluated; pMI, prior myocardial infarction; q.d., once daily; RAS, renin-angiotensin system; SBP, systolic blood pressure.
All patients enrolled in this study were Japanese outpatients.
[a]Assessed in the full analysis set ($N=351$)

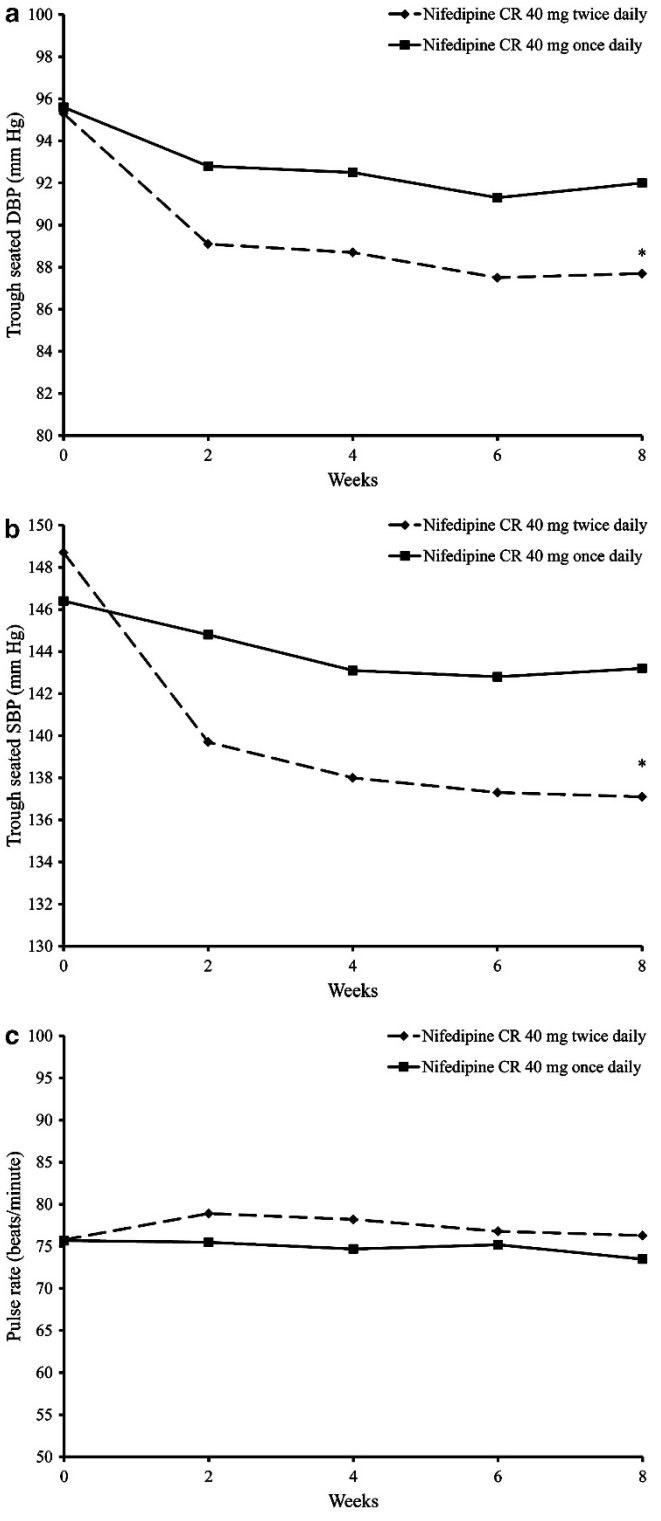

Figure 3 Change from baseline in (**a**) trough seated diastolic blood pressure (DBP), (**b**) trough seated systolic blood pressure (SBP) and (**c**) pulse rate over time in the full analysis set. *$P<0.0001$.

with baseline. However, although the mean pulse rate increased by 3.3 beats min^{-1} with nifedipine CR 40 mg b.i.d. at treatment week 2, it gradually returned to baseline levels by week 8 (increase of 0.7 beats min^{-1} from baseline).

Table 2 SBP/DBP, achievement and responder rates with nifedipine CR 40 mg twice daily (b.i.d.) and nifedipine CR 40 mg once daily (q.d.) in the full analysis set

At 8 weeks	*Nifedipine CR 40 mg b.i.d.*	*Nifedipine CR 40 mg q.d.*
Baseline SBP(s.d.)/DBP(s.d.) mm Hg		
Total	148.7 (11.4)/95.3 (6.1)	146.4 (11.7)/95.6 (6.2)
Elderly (≥65 years old)[a]	155.5 (10.7)/94.7 (5.3)	155.2 (12.5)/94.3 (4.3)
Non-elderly (<65 years)[a]	146.6 (10.7)/95.5 (6.1)	145.0 (11.1)/95.8 (6.3)
Patients with DM, CKD or pMI	152.3 (11.9)/95.0 (6.9)	147.6 (11.8)/96.1 (7.6)
Week 8 SBP/SBP		
Total	137.4 (12.2)/87.9 (8.4)	143.3 (13.8)/92.1 (9.6)
Elderly (≥65 years old)[a]	139.7 (14.1)/83.6 (9.5)	152.9 (17.9)/88.8 (10.1)
Non-elderly (<65 years)[a]	135.8 (10.8)/88.5 (8.1)	141.5 (12.4)/92.3 (9.4)
Patients with DM, CKD or pMI	142.8 (14.6)/88.9 (7.6)	145.9 (15.0)/93.6 (9.7)
Achievement rate, n/N (% patients)[b]		
Total	38/177 (21.5)	18/174 (10.3)
Elderly (≥65 years old)[a]	12/25 (48.0)	4/19 (21.1)
Non-elderly (<65 years)[a]	25/126 (19.8)	14/135 (10.4)
Patients with DM, CKD or pMI	1/26 (3.8)	0/20
Responder rate, n/N (% patients)[c]		
Total	75/177 (42.4)	34/174 (19.5)
Elderly (≥65 years old)[a]	16/25 (64.0)	5/19 (26.3)
Non-elderly (<65 years)[a]	50/126 (39.7)	28/135 (20.7)
Patients with DM, CKD or pMI	9/26 (34.6)	1/20 (5.0)

Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; *N*, total number of patients evaluated; pMI, prior myocardial infarction.
[a]The elderly and non-elderly subpopulations did not include patients with DM, CKD or pMI.
[b]An achievement rate was defined as the proportion of patients achieving blood pressure targets according to JSH 2009 guidelines. This was a SBP/DBP of <140/90 mm Hg in the elderly, <130/85 mm Hg in the non-elderly and <130/80 mm Hg in patients with DM, CKD or pMI.
[c]A responder rate was defined as the proportion of patients achieving blood pressure targets according to the JSH 2009 guidelines or a >10 mm Hg reduction of DBP from baseline.

Safety

Adverse events that were considered to be related to the study drug were reported in 9.0% and 9.7% of patients receiving nifedipine CR 40 mg b.i.d. and q.d., respectively; none of these were considered serious (Table 3).

The frequency of the drug-related adverse events commonly reported with nifedipine CR was low and similar between treatment groups. These included headache (1.7% *vs.* 0%), hot flush (0.6% in each treatment group), palpitations (0% *vs.* 0.6%), peripheral edema (0.6% *vs.* 1.1%), hypotension (0% *vs.* 0.6%), dizziness (0% *vs.* 0.6%) and postural dizziness (0.6% *vs.* 0%). No clinically important differences in routine laboratory parameters were observed between treatment groups. Furthermore, mean changes from baseline in ECG parameters and the incidence of clinically significant ECG findings were similar between treatment groups.

DISCUSSION

In this study, nifedipine CR 40 mg b.i.d. was demonstrated to be an effective treatment in Japanese patients with essential hypertension who did not achieve target BP levels with nifedipine CR 40 mg q.d.

Table 3 Adverse events considered drug-related observed during the double-blind treatment period in the safety analysis set, by primary system organ class

n *(%)*	*Nifedipine CR 40 mg b.i.d.* (N = *177*)	*Nifedipine CR 40 mg q.d.* (N = *175*)	*Total* (N = *352*)
Total	16 (9.0)	17 (9.7)	33 (9.4)
Cardiac disorders	1 (0.6)	1 (0.6)	2 (0.6)
Palpitations	0	1 (0.6)	1 (0.3)
Prinzmetal angina	1 (0.6)	0	1 (0.3)
Gastrointestinal disorders	3 (1.7)	3 (1.7)	6 (1.7)
Constipation	2 (1.1)	2 (1.1)	4 (1.1)
Dyspepsia	0	1 (0.6)	1 (0.3)
Gingival hypertrophy	1 (0.6)	0	1 (0.3)
General disorders and administration site conditions	1 (0.6)	2 (1.1)	3 (0.9)
Peripheral edema	1 (0.6)	2 (1.1)	3 (0.9)
Hepatobiliary disorders	1 (0.6)	1 (0.6)	2 (0.6)
Abnormal hepatic function	1 (0.6)	1 (0.6)	2 (0.6)
Investigations	3 (1.7)	4 (2.3)	7 (2.0)
Increased ALT	1 (0.6)	0	1 (0.3)
Increased alkaline phosphatase	1 (0.6)	0	1 (0.3)
Decreased BP	1 (0.6)	0	1 (0.3)
Blood urine present	0	2 (1.1)	2 (0.6)
Decreased hemoglobin	0	1 (0.6)	1 (0.3)
Increased platelet count	0	1 (0.6)	1 (0.3)
Metabolism and nutrition disorders	1 (0.6)	2 (1.1)	3 (0.9)
Hyperuricaemia	1 (0.6)	0	1 (0.3)
Hypokalaemia	0	1 (0.6)	1 (0.3)
Type 2 diabetes mellitus	0	1 (0.6)	1 (0.3)
Musculoskeletal and connective tissue disorders	2 (1.1)	0	2 (0.6)
Arthralgia	1 (0.6)	0	1 (0.3)
Muscle spasms	1 (0.6)	0	1 (0.3)
Nervous system disorders	4 (2.3)	1 (0.6)	5 (1.4)
Dizziness	0	1 (0.6)	1 (0.3)
Postural dizziness	1 (0.6)	0	1 (0.3)
Headache	3 (1.7)	0	3 (0.9)
Reproductive system and breast disorders	1 (0.6)	0	1 (0.3)
Prostatitis	1 (0.6)	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	0	1 (0.6)	1 (0.3)
Allergic rhinitis	0	1 (0.6)	1 (0.3)
Vascular disorders	1 (0.6)	2 (1.1)	3 (0.9)
Hot flush	1 (0.6)	1 (0.6)	2 (0.6)
Hypotension	0	1 (0.6)	1 (0.3)

Abbreviations: ALT, alanine aminotransferase; b.i.d., twice daily; BP, blood pressure; *n*, number of patients with event; *N*, total number of patients evaluated; q.d., once daily.

After 8 weeks of treatment, patients receiving nifedipine CR 40 mg b.i.d. had a significantly greater reduction in both trough seated DBP and SBP compared with nifedipine CR 40 mg q.d.. The differences in BP between treatment groups were observed as early as 2 weeks into treatment and were maintained over the double-blind treatment period. These results support the findings of a recently published phase II study which compared the efficacy and tolerability of nifedipine CR 80 mg per day (40 mg b.i.d. or 80 mg q.d.) with 40 mg q.d. in 35 patients who did not achieve target BP levels with nifedipine CR 40 mg q.d.[15] This randomized, double-blind, crossover trial showed that nifedipine 40 mg b.i.d. improved treatment outcomes and also highlighted that the best treatment regimen for high-dose nifedipine CR was 40 mg b.i.d. as the plasma concentrations of nifedipine were higher at trough in this treatment arm. Based on that study, it was decided to use nifedipine 40 mg b.i.d., not 80 mg q.d. in this phase III trial.

In this phase III study, considering those who achieved target BP levels or were considered to be 'responders' at 8 weeks, the number of patients receiving nifedipine CR 40 mg b.i.d. was approximately twofold that of the patients receiving nifedipine CR 40 mg q.d. (21.5% and 42.4% *vs.* 10.3% and 19.5%, respectively). However, less than 50% of patients receiving nifedipine CR 40 mg b.i.d. were considered responsive. This was an unexpected result as other trials of nifedipine in other patient populations showed higher responder rates.[16] These low achievement rates observed in the current study may be explained by the fact that the enrolled patients were those who had already received nifedipine CR 40 mg q.d. but still had uncontrolled BP, and were not hypertensive therapy-naïve patients. Thus patients in the current study were refractory to antihypertensive agents, which may account for the relatively low BP target achievement and responder rates. In addition, patients did not receive antihypertensive agents other than nifedipine during this study.

In this trial, 36 patients had DM and 12 patients had CKD (Table 1). We did not analyze according to each complication, however, the blood pressures in the patients with DM, CKD and pMI were changed from 152.3 (11.9)/95.0(6.9) to 142.8 (14.6)/88.9 (7.6) mm Hg with 40 mg b.i.d. and slightly changed from 147.6(11.8)/96.1(7.6) to 145.9(15.0)/93.6(9.7) mm Hg with 40 mg q.d. (Table 2). Also, patients who had DM, CKD or pMI had lower BP target achievement rates than patients without these comorbid conditions (Table 2). This highlights the recent findings of studies that have shown that the target BP achievement rate in hypertension patients with comorbidities remains low, particularly in patients with DM, despite extensive research in this area.[7,8] The JSH 2009 guidelines recommend, that when BP is not adequately controlled with monotherapy, other agents are added, especially among patients at high risk, such as those with DM, CKD or pMI.

Although nifedipine CR 40 mg b.i.d. was associated with marked BP reductions, up-titrating nifedipine CR was generally well tolerated, with the incidence of drug-related adverse events being similar between both nifedipine CR doses and no unexpected adverse events being reported. The frequency of adverse events commonly reported with antihypertensives is low and similar between nifedipine CR 40 mg b.i.d. and q.d. Similar results were obtained in a recent, small retrospective study of nifedipine CR 80 mg per day, which showed that treatment with the higher dose of nifedipine CR in patients with essential hypertension who were uncontrolled by previous antihypertensive therapy was well tolerated for up to 24 months.[17] Of interest, the reported incidence of hypotension in our study was low. This is because, although nifedipine significantly reduces BP in hypertensive patients, it only mildly decreases BP in normotensive patients.[18] This is thought to be due to the mechanism of action of CCBs, which inhibits intracellular Ca^{2+} influx.[19]

It is well-known that the nifedipine capsule may temporarily increase the pulse rate in patients who are highly sensitive to CCBs as a result of their potent peripheral vasodilatory effect[20–22] and thus

in the present study, it was expected that increasing the dosage of nifedipine CR may temporarily increase the pulse rate of these patients. However, changes in the pulse rate over the treatment period were similar between the two doses. This may be because the patients enrolled in this trial were not CCB naïve and they had already received nifedipine CR 40 mg q.d. during the screening period. Furthermore, it appears that long-acting CCBs enhance the sympathetic system to a lesser extent than short-acting CCBs. The study by Minami *et al.*[12] demonstrated that the long-acting formulation of nifedipine (nifedipine CR) has less influence on the autonomic nervous system than nifedipine retard. Interestingly, these results were consistent with those of a phase III study of similar design investigating the effects of an increased dosage of amlodipine (10 mg per day); similar nonsignificant changes in pulse rate between a lower and higher amlodipine dose were reported.[23]

There are some limitations to this study. This study investigated the efficacy and tolerability of nifedipine CR 40 mg b.i.d. in a regulated setting. Seated BP assessments were conducted in an office when nifedipine concentrations were at trough levels. However, although measurements of office seated BP are suitable, measurements of home BP, 24-h ambulatory BP monitoring, night BP, sleeping BP and visit-to-visit variability of BPs are also essential to gain a full picture of the antihypertensive effect of a treatment. Finally, this study was not an active-controlled study and had a study period of only 8 weeks. To fully elucidate the beneficial effect of nifedipine CR 40 mg b.i.d., further studies investigating this dose in a real-world setting are essential. In particular, the use of nifedipine CR in combination with other antihypertensive or concomitant medications, studies comparing nifedipine CR 40 mg b.i.d. with other high-dose antihypertensive monotherapies (such as amlodipine 10 mg per day), combination therapies and long-term observational studies are warranted.

In conclusion, administration of a higher dose of nifedipine CR (40 mg b.i.d.) was associated with greater efficacy and a safety profile similar to that of the currently approved dose (40 mg q.d.) in Japanese patients with essential hypertension, and it may offer treatment choice for patients who do not achieve target BP levels with nifedipine CR 40 mg q.d.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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