The Effects of the L/N-Type Calcium Channel Blocker (Cilnidipine) on Sympathetic Hyperactive Morning Hypertension: Results From ACHIEVE-ONE*

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The Ambulatory Blood Pressure Control and Home Blood Pressure (Morning and Evening) Lowering By N-Channel Blocker Cilnidipine (ACHIEVE-ONE) trial is a large-scale clinical study on blood pressure (BP) and pulse rate (PR) in the real world with use of cilnidipine, a unique L/N-type Ca channel blocker, possessing a suppressive action on increased sympathetic activity in patients with essential hypertension. The effects of cilnidipine on morning hypertension were examined. The authors examined 2319 patients treated with cilnidipine for 12 weeks. Clinic systolic BP (SBP) decreased by 19.6 mm Hg from 155.0 mm Hg, whereas morning SBP decreased by 17.0 mm Hg from 152.9 mm Hg after 12-week cilnidipine treatment. Cilnidipine reduced both morning SBP and PR more markedly in patients with higher baseline morning SBP (−3.2 mm Hg and −1.3 beats per minute in the first quartile of morning SBP, −30.9 mm Hg and −3.2 beats per minute in the fourth quartile), and also reduced both morning PR and SBP more markedly in patients with higher baseline morning PR (0.6 beats per minute and −15.6 mm Hg in <70 beats per minute, and −9.7 beats per minute and −20.2 mm Hg in ≥85 beats per minute). Cilnidipine significantly reduced BP and PR in hypertensive patients at the clinic and at home, especially with higher BP and PR in the morning. *J Clin Hypertens (Greenwich).* 2013; 15:133–142. ©2012 Wiley Periodicals, Inc.

In recent years, it has been demonstrated that home or 24-hour blood pressure (BP) monitoring predicts the risk of cardiovascular events.[1–3] Home BP measurements have been rapidly spreading because of its simple approach. Home morning hypertension is associated with a risk for chronic kidney disease and cardiovascular events.[4,5] In addition, an elevated pulse rate (PR) is associated with a risk for cardiovascular morbidity and mortality.[6,7] Therefore, management of morning hypertension and high PR is important in preventing cardiovascular events. Cilnidipine has two actions[8,9]: block L-type Ca channels in vascular smooth muscle, which exerts an antihypertensive effect similar to L-type Ca channel blockers (eg, amlodipine), and block N-type Ca channels at sympathetic nerve endings, which suppresses increased sympathetic activity in animal models[9–11] and humans.[12–14] In this manner, cilnidipine is an effective Ca channel blocker to treat morning hypertension characterized by increased sympathetic activity in the early morning. Amlodipine, an L-type Ca channel blocker, reduced BP, but its PR-lowering effect is controversial.[15–17] In contrast, several studies demonstrated that cilnidipine reduced not only BP but also PR.[18,19] PR is influenced by both sympathetic and parasympathetic activities. Increased sympathetic activity leads to high PR. We are interested in whether cilnidipine is effective on not only higher BP, but also higher PR in hypertensive patients in the real world. The Ambulatory Blood Pressure Control and Home Blood Pressure (Morning and Evening) Lowering by N-Channel Blocker Cilnidipine (ACHIEVE-ONE) trial is a large-scale clinical study designed to evaluate the clinical effects of cilnidipine on BP and PR measured at the clinic, at home, and by ambulatory BP monitoring (ABPM) in patients with essential hypertension in daily medical practice. Previously, another large-scale clinical study was reported that cilnidipine reduced BP and PR at the clinic in hypertensive patients.[18] In this study, we examined the effects of cilnidipine on home BP and PR in hypertensive patients in the real world.

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METHODS

Patients and Study Design

This study was approved by the institutional review board of Jichi Medical University and was registered

with the University Medical Information Network Clinical Trials Registry, Japan (UMIN000003695). This study was conducted in conformity with the Japanese Good Post-Marketing Study Practice, which is a regulation of post-marketing surveillance activities.

Clinical practitioners were openly recruited from across Japan. Patients had hypertension and accepted cilnidipine medication in daily medical practice during the period from October 2008 to September 2010. Pregnant women and women suspected of being pregnant were excluded from this study, but no restriction was set on age or complications. Each clinical practitioner participating in this study registered hypertensive patients with PostMaNet, an electric data capturing system developed by Fujitsu F.I.P. Corporation (Tokyo, Japan) within 2 weeks of starting cilnidipine treatment and uploaded follow-up data on each patient into the system. No written informed consent was required, since this was an observational study in daily medical practice, not an interventional study. Cilnidipine is a Ca channel blocker approved in Japan for its use according to the following administration and dosage regimen: (1) for patients with hypertension at a once-daily oral treatment after breakfast at a dose of 5 to 10 mg, and (2) for patients with severe hypertension at a dose that can be increased up to 20 mg. Regimens for cilnidipine and other concomitant drugs had been decided by practitioners with their patient's agreement and were not changed until the study was finished, except for patients suffering therapeutic disadvantage. Adverse effects encountered in this study were collected with an electronic data capture system based on report from practitioners. Practitioners trained each patients on how to measure home BP as recommended by the guideline of the Japanese Society of Hypertension.[20] Each patient recorded home BP in a notebook specialized for BP management. During this study, each patient used an electronic cuff oscillometric device that had been approved by the Ministry of Health, Labor, and Welfare, Japan. Individual baseline data of BP and PR at home were determined as a 3-day average of BP and PR measured once early in the morning (hereinafter called "morning") and once just before going to bed (hereinafter called "evening") before starting treatment. Baseline clinic BP and PR were measured once before starting treatment. Home BP and PR in the morning before medication and evening after medication and clinic BP and PR at each visit were measured once at weeks 4, 8, and 12 of treatment.

Statistical Analysis

To estimate sample size for an analysis of relationship between stratified SBP in the morning (MSBP) and PR in the morning (MPR), we assumed that cilnidipine reduced average MPR by 0.5, 1.0, 1.5, 2.5 beats per minute (bpm) in the first, second, third, and fourth quartiles, respectively, of MSBP with 10 bpm standard deviation (SD) of MPR as referenced by another study that cilnidipine reduced PR by 1.2 bpm with SD by 10 bpm.[18] Using these estimated data, sample size in this study was calculated as a total of 2000 patients performed by the one-way analysis of variance (ANOVA) with two-sided significance, because 500 patients in each quartile were required to achieve a minimum statistical power of 80%. Data are expressed as mean±SD unless otherwise noted. Evening SBP (ESBP) subtracted from MSBP of the same day was defined as the morning-evening SBP difference (Di-ME-SBP). The average of MSBP and ESBP was defined as the mean morning-evening SBP (Ave-ME-SBP). An unpaired *t* test was carried out to evaluate differences in baseline values of MSBP and the degree of changes in clinic SBP (CSBP) and MSBP. A Dunnett test was employed to analyze changes in BP and PR after starting treatment. A paired *t* test or a Wilcoxon signed rank sum test was used for comparison of BP and PR between pretreatment and post-treatment values. A Fisher exact test was used in the analysis of changes in patient distribution, and a one-way ANOVA was employed for the analysis of changes in MSBP, MPR, and Di-ME-SBP in relation to the value of MSBP, MPR, and Di-ME-SBP at baseline. In all tests, $P<.05$ (two-tailed) was regarded as significant.

RESULTS

Baseline Characteristics

Patient characteristics are shown in Table I. This report covers data from 2319 patients who had baseline MSBP values in the ACHIEVE-ONE study. Among them, 171 patients had no MSBP values during cilnidipine treatment. There was no significant difference in baseline MSBP values between the group of 171 patients and the others who measured MSBP at least once during treatment (152.8±18.6 vs 152.9±16.1 mm Hg, respectively, $P=.971$). Of 171 patients, there were patients who measured CSBP during the treatment. The effects of cilnidipine on CSBP in the two groups showed no significant differences (eg, changes from baseline after 12 weeks were −19.0±22.0 mm Hg [n=65] and −19.3±19.9 mm Hg [n=1876] for 171 patients and the patients who measured MSBP, respectively, $P=.911$).

Cilnidipine Treatment

In this study, cilnidipine was prescribed once daily in the morning for 1792 (77.3%) patients, once daily in the evening for 267 (11.5%) patients, and twice daily in the morning and evening for 260 (11.2%) patients, with a mean daily dose level being 10.6±3.9 mg.

Changes in BP and PR at the Clinic and at Home

SBP and diastolic BP (DBP) decreased significantly after 4 weeks and thereafter, either at the clinic or at home (Figure 1). Changes from baseline after 12 weeks were −19.6, −17.0, and −13.6 mm Hg, for

TABLE I. Characteristics of Patients

Baseline characteristics of patients, No.	2319
Age, y	67.8±12.0
BMI, kg/m^2	23.9±3.6
Men, No. (%)	1271 (54.8)
Comorbidity, No. (%)	1704 (73.5)
Dyslipidemia, No. (%)	566 (24.4)
Ischemic heart disease, No. (%)	435 (18.8)
Diabetes mellitus, No. (%)	353 (15.2)
Cerebral vascular disorder, No. (%)	188 (8.1)
Chronic kidney disease, No. (%)	156 (6.7)
Cilnidipine monotherapy during the study, No. (%)	812 (35.0)
Combination therapy during the study, No. (%)	1507 (65.0)
Concomitant antihypertensive drug	
ARB, No. (%)	1082 (46.7)
Diuretic, No. (%)	303 (13.1)
β-Blocker, No. (%)	195 (8.4)
αβ-Blocker, No. (%)	176 (7.6)
CCB, No. (%)	171 (7.4)
ACE inhibitor, No. (%)	131 (5.6)
α-Blocker, No. (%)	61 (2.6)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker. Age and body mass index (BMI): mean±standard deviation.

CSBP, MSBP, and ESBP, respectively. Moreover, PR decreased significantly after 4 weeks both at the clinic and at home (Figure 1).

At baseline, 76.0% of patients were in the sustained hypertension group, CSBP ≥140 mm Hg and MSBP ≥135 mm Hg, but this proportion significantly decreased to 25.4% after 12 weeks (Figure 2). The ratio of patients in the well controlled group, CSBP <140 mm Hg and MSBP <135 mm Hg, rose significantly from 5.7% to 35.9% (Figure 2).

Morning SBP at baseline was divided into quartiles, and changes in MSBP and MPR were compared among the quartiles. Results revealed that the higher the MSBP at baseline, the greater MSBP ($P<.0001$, Figure 3a and 3b) and MPR ($P=.0077$, Figure 3c) was reduced. In contrast, the higher baseline ESBP, the more ESBP was reduced ($P<.0001$), with the exception of evening PR ($P=.0868$) (data not shown). The same significant reduction pattern was also observed when the relation was analyzed by percentage of reduction. The percentage value of each quartile from MSBP quartile 1 (Q1) to MSBP quartile 4 (Q4), was −2.1, −9.0, −12.5, and −17.7 for MSBP ($P<.0001$) and −1.1, −1.8, −2.5, and −3.6 for MPR, ($P=.0146$), respectively. Morning PR at baseline was divided into three categories (<70, ≥70 but <85, and ≥85 bpm) from three studies. A study by Ohasama[21] reported that even in normotensive patients whose MSBPs were <135 mm Hg, the risk for individuals with MPR ≥70 bpm to develop cardiovascular mortality was about double. In addition, the group with higher PR was subdivided into two groups according to the result of a Framingham study[7] that the cardiovascular and all cause mortality risks for individuals with heart rate ≥85 bpm was higher than <85 bpm. The Norway prospective study[22] demonstrated that an increase in PR was associated with increased risk of death from ischemic heart disease and for all-cause mortality, when PR was divided into three categories, <70, ≥70 but <85, and ≥85 bpm. It was revealed that the higher the baseline MPR, the greater MPR was

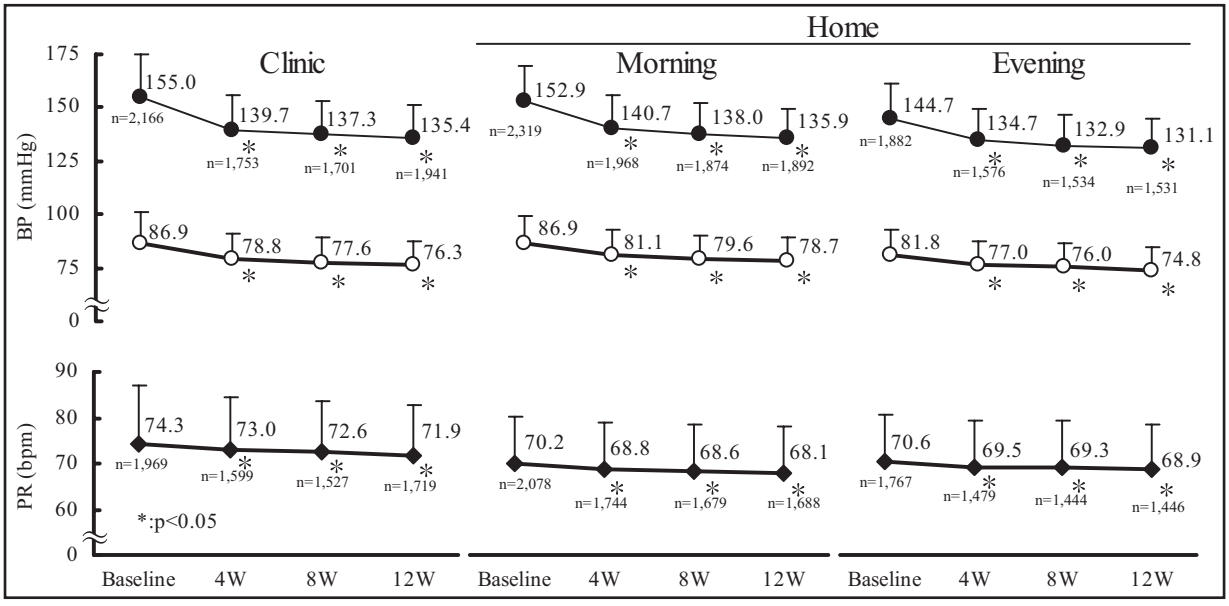

FIGURE 1. Changes in blood pressure (BP) and pulse rate (PR) at the clinic and at home. W indicates week; bpm, beats per minute; • systolic BP;○ diastolic BP; ♦ PR. *$P<.05$ vs baseline.

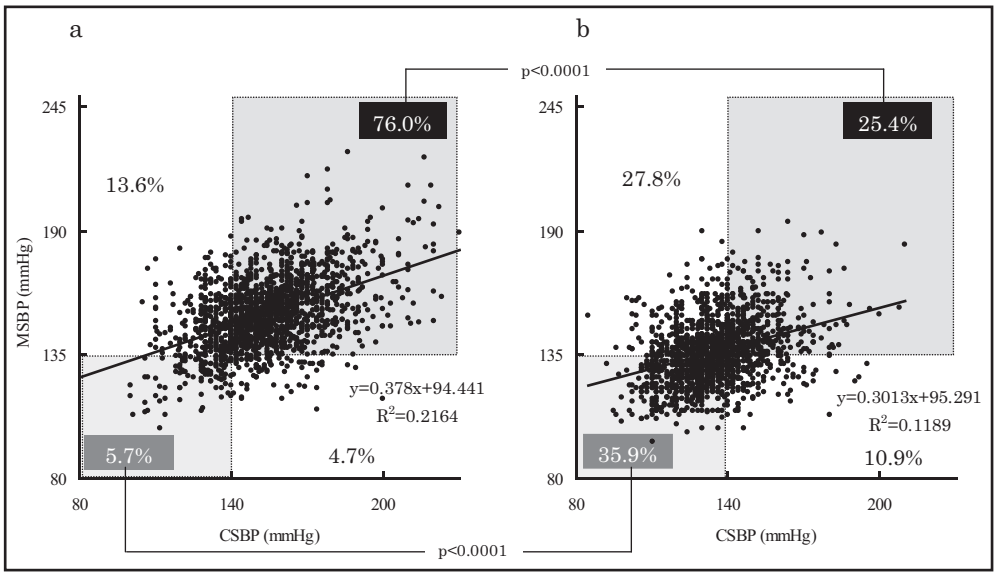

FIGURE 2. Changes in the percentages of patients categorized by clinic systolic blood pressure (CSBP) and mean systolic blood pressure (MSBP) at baseline (a) and after 12 weeks of treatment (b).

reduced (Figure 3d and 3e). Furthermore, the higher the baseline MPR, the greater MSBP was reduced (Figure 3f). The same significant reduction pattern was also observed when the relation was analyzed by percentage reduction. The percent value of each category, from MPR <70 bpm to MPR ≥85 bpm, was 1.3, −4.7, and −10.6 for MPR, ($P<.0001$) and −9.7, −10.6, and −12.4 for MSBP ($P<.0106$), respectively.

To exclude the possibility that BP- and PR-lowering effects of cilnidipine accounted only for consequence of phenomenon of regression to the mean, we examined the changes in BP and PR in patients treated with cilnidipine in relation to stratified BP and PR at baseline. When each of the four groups divided by MSBP quartiles (MSBPQ1-Q4) was subdivided into two groups by a cutoff MPR level of 70 bpm, changes in MSBP after treatment were significantly greater in patients with MPR ≥70 bpm than in patients with MPR <70 bpm in the MSBPQ4 group, while in the other lower MSBP groups (MSBPQ1–Q3) there were no significant differences in changes in MSBP between the MPR subgroups (Figure 4). It is also noted that MSBP and MPR at home had little correlation with each other at baseline (r=0.095), after 12-week treatment (r=−0.012), or in amount of changes (r=0.101) by Spearman's correlation coefficient analysis.

Among patients with morning hypertension (MSBP ≥135 mm Hg), the percentage of patients with high MPR (≥70 bpm) decreased significantly from 46.5% at baseline to 24.4% after 12 weeks ($P<.0001$, not shown).

Significant decreases in MSBP and MPR were also seen when β-blockers were concomitantly used (Table II). While MSBP and MPR decreased significantly by 17.3 mm Hg from 153.3±15.7 mm Hg and by 2.1 bpm from 70.7±10.3 bpm without β-blockers, they also decreased significantly by 13.7 mm Hg from 149.3±16.2 mm Hg and by 1.8 bpm from 67.0±10.8 bpm, respectively, with β-blockers after 12 weeks. Similar results were also observed in patients without concomitant antihypertensive drug use as well as in patients with or without angiotensin receptor blockers (ARBs), and angiotensin-converting enzyme (ACE).

Changes in Ave-ME-SBP and Di-ME-SBP

We previously reported that the percentages of elderly people, drinkers, and β-blocker users were higher in the group with Di-ME-SBP ≥15 mm Hg than that with <15 mm Hg in medicated hypertensive patients.[23] Therefore, it was desirable to manage the Di-ME-SBP below 15 mm Hg even in hypertensive patients whose CSBP were well controlled.[23] In the present study, the percentage of patients with Ave-ME-SBP ≥135 mm Hg decreased significantly from 85.1% at baseline to 43.1% after 12 weeks, and that of patients with Ave-ME-SBP ≥135 mm Hg and Di-ME-SBP ≥15 mm Hg decreased significantly from 20.9% to 7.1%. Moreover, normotensives with Ave-ME-SBP <135 mm Hg and Di-ME-SBP <15 mm Hg rose significantly from 10.6% to 45.8% (Figure 5).

When Di-ME-SBP at baseline was divided into quartiles, it was revealed that the higher the baseline Di-ME-SBP, the more Di-ME-SBP decreased. In contrast, in the case that baseline Di-ME-SBP was <0.7 mm Hg, in which patients whose ESBP was higher than MSBP were included, Di-ME-SBP increased (Figure 6).

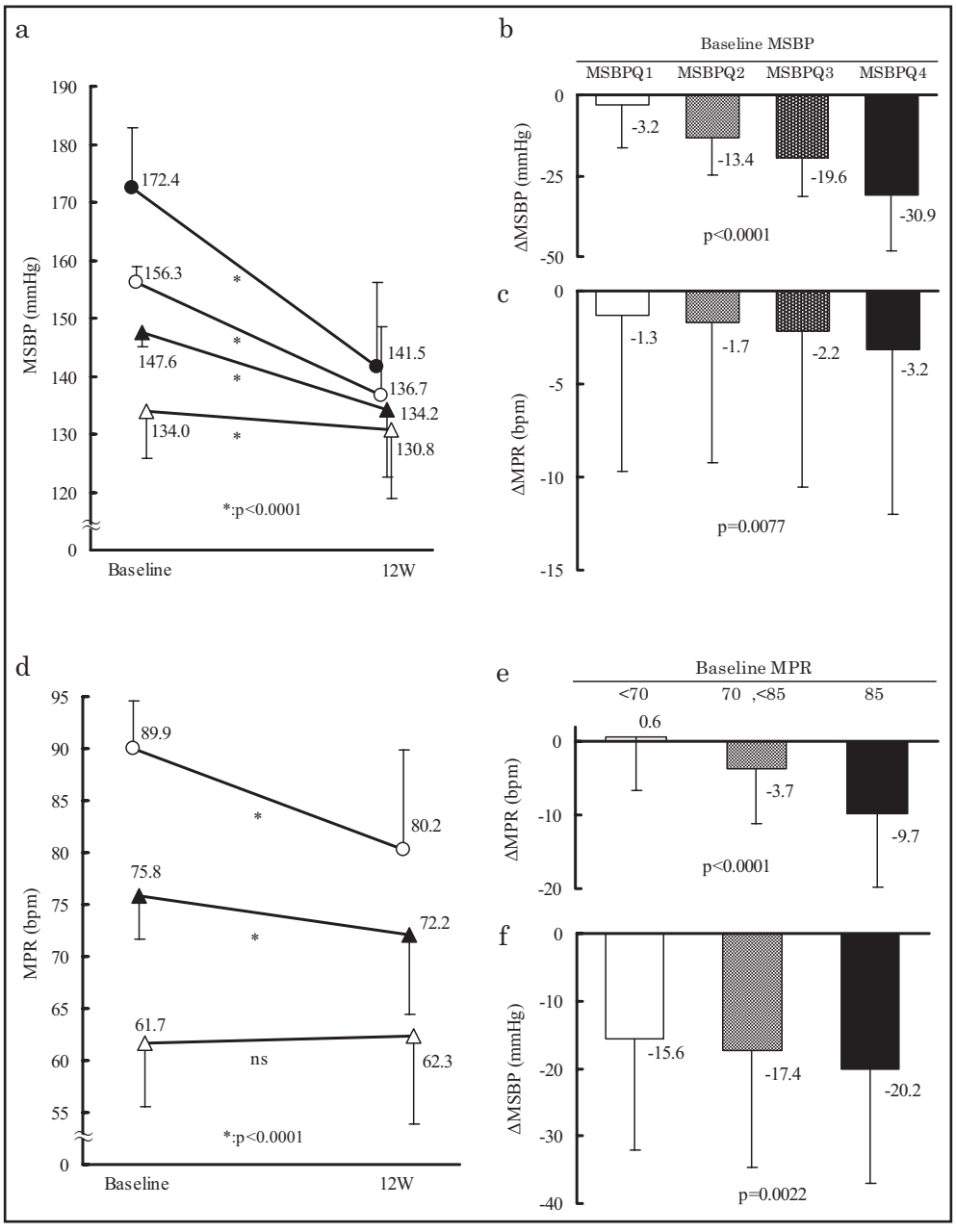

FIGURE 3. Changes in mean systolic blood pressure (MSBP) and mean pulse rate (MPR) in relation to baseline mean systolic blood pressure (MSBP) quartiles and changes in MPR and MSBP in relation to baseline MPR. MSBP quartile 1 (Q1): MSBP <142.7 mm Hg, MSBP quartile 2 (Q2): MSBP ≥142.7 but <151.7 mm Hg, MSBP quartile 3 (Q3): MSBP ≥151.7 but <161.3 mm Hg, MSBP quartile 4 (Q4): MSBP ≥161.3 mm Hg. Comparison of MSBP between baseline and after 12 weeks of treatment (12W) (a). MSBP quartiles: MSBPQ1 (Δ); MSBPQ2 (▲); MSBPQ3 (○); MSBPQ4 (•). (b) Changes in MSBP from baseline to after 12 weeks of treatment (b). Changes in MPR from baseline to after 12 weeks of treatment (c). Comparison of MPR between baseline and after 12 weeks of treatment (d). MPR: <70 beats per minute (bpm) (Δ); ≥70 but <85 bpm (▲); ≥85 bpm (○). Changes in MPR from baseline to after 12 weeks of treatment (e). Changes in MSBP from baseline to after 12 weeks of treatment (f).

Adverse Reactions Related to Cilnidipine

A total of 63 episodes of adverse reactions occurred in 59 patients (2.54%). Major adverse reactions were dizziness (8 episodes, 0.34%), hypotension (5 episodes, 0.22%), flushing (4 episodes, 0.17%), hot flushes (4 episodes, 0.17%), and palpitations (4 episodes, 0.17%).

DISCUSSION

ACHIEVE-ONE is a large-scale clinical study on hypertensive patients. The study demonstrated that a unique L/N-type Ca channel blocker, cilnidipine, reduced both MSBP and MPR more markedly in patients with higher MSBP at baseline, and those with

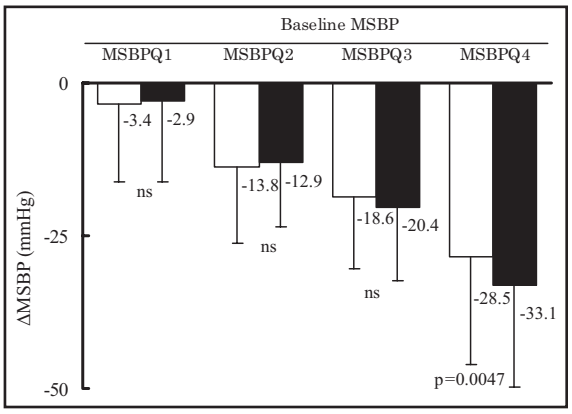

FIGURE 4. Changes in mean systolic blood pressure (MSBP) in relation to MSBP quartile and mean pulse rate (MPR) categories at baseline. MSBP quartile 1 (Q1): MSBP <142.7 mm Hg; MSBP quartile 2 (Q2): MSBP ≥142.7 but <151.7 mm Hg; MSBP quartile 3 (Q3): MSBP ≥151.7 but <161.3 mm Hg; MSBP quartile 4 (Q4): MSBP ≥161.3 mm Hg. MPR: <70 bpm (□); ≥70 beats per minute (bpm) (■). ns indicates not significant.

both MPR and MSBP more markedly in patients with higher MPR at baseline. These effects of cilnidipine are new features not known in conventional L-type Ca channel blockers. We speculated that cilnidipine suppressed increased sympathetic activity in the morning by independent BP- and PR-lowering effects through neuronal N-type Ca channel blocking in addition to L-type Ca channel blocking.[8,9]

The percentage of patients with baseline MSBP >135 mm Hg was 90% in the present study and 94% in an add-on study of amlodipine 5 to 10 mg daily.[24] MSBP decreased by 17 mm Hg from 152.9 mm Hg in the present study and by 16 mm Hg from 151.5 mm Hg in the add-on study of amlodipine. In addition, similar to conventional L-type Ca channel blockers, cilnidipine reduced MSBP more markedly in patients with higher MSBP at baseline. The BP-lowering effect through L-type Ca channel blocking of cilnidipine was comparable to that of amlodipine. This result may involve a consequence of the regression to the mean. However, cilnidipine reduced MSBP more markedly in patients with higher MPR at baseline and also reduced MPR more markedly in patients with higher MSBP at baseline. Furthermore, as shown in Figure 4, reductions in MSBP were significantly greater in the high MPR (≥70 bpm) group than the low (<70 bpm) MPR group, only at the top quartile of MSBP at baseline. Given that regression to the mean was the only factor that led to BP lowering, there was no difference between the PR groups (Figure 4). Therefore, the BP-lowering effect of cilnidipine in the morning hypertension group (MSBPQ4) with high MPR (≥70 bpm) was one of the effects of cilnidipine itself.

Generally, morning hypertension involves increased sympathetic activity[25,26] and the renin-angiotensin system (RAS).[28] Cilnidipine reduced MSBP and MPR even in patients who had already been administrated β-blockers or RAS inhibitors (including ARBs and ACE inhibitors). These additive BP- and PR-lowering effects of cilnidipine may be a reflection of dual L-and N-type Ca channel–blocking actions differing from β-adrenergic receptor blocking and RAS-inhibiting actions (Table II). Cilnidipine would be an optimal Ca channel blocker for patients with ''high rate morning hypertension'' characterized by high MSBP and MPR.

It has been reported that elevated PR is a risk for cardiovascular events.[29,30] Recently, a large population cohort of apparently healthy men and women showed that an increase in resting PR from <70 bpm to >85 bpm during a 10-year period was associated with a 1.9-fold higher risk of death from ischemic heart disease.[22] In addition, ivabradine, a selective PR-lowering drug, has been reported to reduce cardiovascular mortality or hospitalization of patients with heart failure.[31] The PR-lowering effect of cilnidipine has been confirmed by several reports,[18,19,32] although that of amlodipine is controversial,[15–17] significant PR reduction was not observed in the open-label repeated studies in patients treated with L-type Ca channel blockers, amlodipine,[33] lercanidipine, and nifedipine GITS.[34] Cilnidipine lowered MPR only in the high MPR group. In hypertensive patients with PR <70 bpm, even if they had increased sympathetic

TABLE II. Changes in MSBP and MPR in Relation to Concomitantly Used Hypertensive Drugs

	MSBP				MPR			
	Week 0	Week 12	No.	*P* Value	Week 0	Week 12	No.	*P* Value
Cilnidipine monotherapy	154.6±14.4	135.1±12.1	666	<.0001	71.0±10.6	68.8±10.1	609	<.0001
Combination therapy	151.6±16.4	136.4±14.2	1226	<.0001	69.6±10.2	67.6±10.2	1079	<.0001
RAS inhibitor (–)	153.0±15.5	135.6±12.6	914	<.0001	70.7±10.6	68.5±10.0	823	<.0001
ARB (+)	152.6±16.0	136.4±14.4	895	<.0001	69.5±10.3	67.4±10.1	794	<.0001
ACE inhibitor (+)	149.6±16.5	136.0±12.7	110	<.0001	71.2±10.9	69.4±11.2	96	=.0326
β-Blocker (–)	153.3±15.7	136.0±13.4	1582	<.0001	70.7±10.3	68.6±10.1	1423	<.0001
β-Blocker (+)	149.3±16.2	135.6±14.3	310	<.0001	67.0±10.8	65.2±10.1	265	=.0005

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MPR, morning pulse rate; MSBP, morning systolic blood pressure; RAS, renin-angiotensin system.

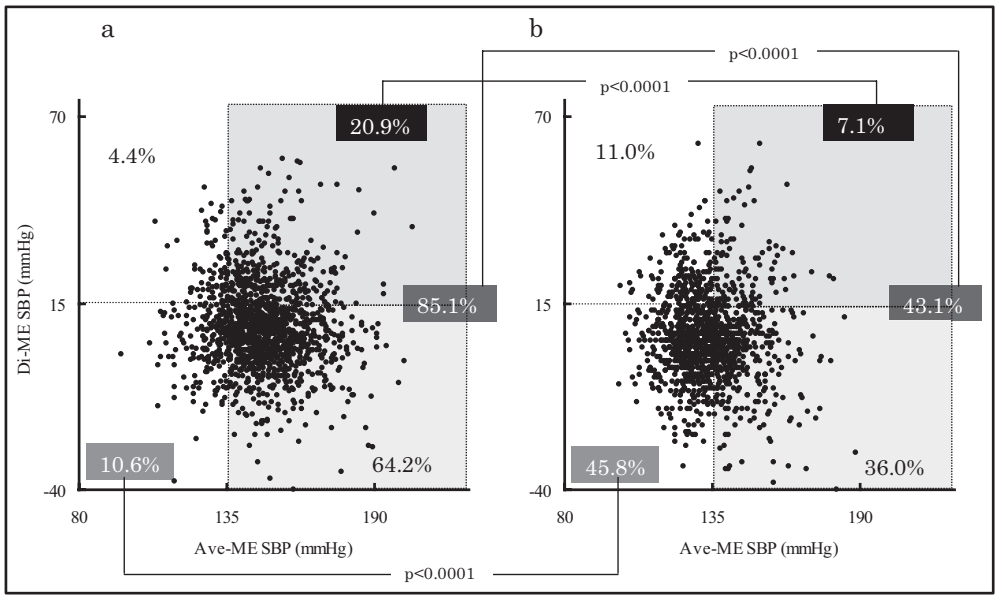

FIGURE 5. Changes in the percentage of patients distributed into four groups categorized by mean morning-evening systolic blood pressure (Ave-ME-SBP) and morning-evening systolic blood pressure difference (Di-ME-SBP) at baseline (a) and after 12 weeks of treatment (12W) (b).

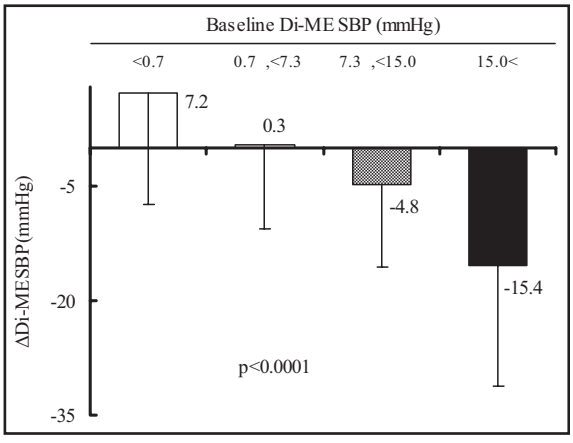

FIGURE 6. Changes in morning-evening systolic blood pressure difference (Di-ME-SBP) in relation to Di-ME-SBP quartiles at baseline.

activity, cilnidipine significantly reduced MSBP but not MPR, suggesting that the L-type channel–blocking action may be predominantly effective compared with the N-type–blocking action in these patients. Therefore, cilnidipine may be still beneficial for future cardiovascular risk for hypertensive patients with low PR as well as those with high PR. It was reported that renal sympathetic denervation significantly lowered BP, but did not reduce PR or plasma noradrenaline levels, and even progressed glomerular hyperfiltration.[35] In addition, the Cilnidipine vs Amlodipine Randomised Trial for Evaluation in Renal Disease (CARTER) study demonstrated that cilnidipine prevented the prognosis of renal disease beyond its BP-lowering effects.[36] Therefore, the combination of cilnidipine and renal sympathetic denervation may achieve better PR control and cardiorenal protection as well as BP control.

In the present study, cilnidipine reduced Di-ME-SBP in patients with baseline Di-ME-SBP >15 mm Hg by MSBP-lowering effects. We demonstrated in our previous report that the percentages of medicated hypertensive patients with older age, regular alcohol drinking, and β-blocker use were higher in the group with Di-ME-SBP >15 mm Hg than in the group with Di-ME-SBP <15 mm Hg.[23] Therefore, it was recommended to keep Di-ME-SBP <15 mm Hg even in patients whose CSBP were well controlled.[23] We also demonstrated that the risk for stroke was 2.1-fold higher in the presence of sustained hypertension (Av-ME-SBP ≥135 mm Hg and Di-ME-SBP <20 mm Hg) and 6.6-fold higher in the presence of morning hypertension (Av-ME-SBP ≥135 mm Hg and Di-ME-SBP ≥20 mm Hg). We speculated that cilnidipine prevents cerebrovascular events in morning hypertensive patients.

STUDY LIMITATIONS

A limitation of this study is that it did not incorporate a control group. Therefore, relative evaluation of the efficacy of cilnidipine was not possible despite the large number of patients enrolled into the study. Each BP measurement device may not be validated. BP data self-measured at home were transcribed to a notebook and reported by patients to practitioners. Therefore, data may potentially include transcription errors and reporting bias.

CONCLUSIONS

This study clarified the characteristics of cilnidipine including greater MSBP reductions in a high MPR (≥70 bpm) group than a low (<70 bpm) MPR group at the top quartile of MSBP at baseline. An L/N-type Ca channel blocker, cilnidipine, significantly reduced BP and PR at the clinic and at home in Japanese hypertensive patients, especially with high BP and high PR in the morning, in a real-world setting.

Acknowledgments and disclosures: Kazuomi Kario, the principal investigator of ACHIEVE-ONE, supervised its conduct and data analysis and had primary responsibility for the writing of this paper. The other authors have read and approved the manuscript of this study. None of the authors received remuneration for performing the study. We are indebted to all those who cooperated with ACHIEVE-ONE and provided valuable data for this study. Details of the members of ACHIEVE-ONE are listed in the Appendix.

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APPENDIX

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