Received: 15 October 2020 | Revised: 21 December 2020 | Accepted: 29 December 2020

DOI: 10.1111/jch.14178

SHORT REPORT

WILEY

# Single-pill combination of cilnidipine, an l-/n-type calcium channel blocker, and valsartan reduces the day-by-day variability of morning home systolic blood pressure in patients with treated hypertension: A sub-analysis of the HOPE-combi survey

Kazuomi Kario MD, PhD[1] | Saori Matsuda BSc[2] | Shinobu Nagahama BSc[2] | Yoshiki Kurose BSc[2] | Hitoshi Sugii BSc[3] | Tsukasa Teshima BA[3] | Noriyuki Suzuki BSc[4]

[1]Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

[2]Post-Marketing Medical Research Group, Medical Department, EA Pharma Co., Ltd., Tokyo, Japan

[3]Post-Marketing Surveillance, Mochida Pharmaceutical Co., Ltd., Tokyo, Japan

[4]Medical Affairs Department, Mochida Pharmaceutical Co., Ltd., Tokyo, Japan

**Correspondence**
Kazuomi Kario, MD, PhD, FACP, FACC, FAHA, FESC, Division of Cardiovascular Medicine, Jichi Medical University School of Medicine, Tochigi, Japan.
Email: kkario@jichi.ac.jp

**Funding information**
This study was funded by EA Pharma Co., Ltd. and Mochida Pharmaceutical Co., Ltd.

## Abstract

We examined the effects of a fixed-dose single-pill combination of cilnidipine (10 mg), an L-/N-type calcium channel blocker, and valsartan (80 mg) (SPC of Cil/Val) on the day-by-day variability of morning home systolic blood pressure (MHSBP) in 616 patients with treated hypertension for 12 months as a sub-analysis of the HOPE-Combi survey, multicentral, post-marketing, and prospective observational survey. The SPC of Cil/Val was administrated once a day in the morning. The SPC of Cil/Val decreased the standard deviation (SD, from 6.3 ± 4.8 to 5.1 ± 3.8 mmHg, $p < .01$), coefficient of variation (from 4.3 ± 3.2 to 3.8 ± 2.9%, $p < .05$), average real variability (ARV, from 7.9 ± 6.6 to 6.3 ± 5.1 mmHg, $p < .01$), and the difference between maximum and minimum (MMD, from 11.9 ± 9.2 to 9.7 ± 7.2 mmHg, $p < .01$) of MHSBP. The variability of MHSBP increased with age; however, this was not increased in patients ≥70 years at the baseline. In elderly patients (≥70 years, $N = 283$), the SPC of Cil/Val decreased the SD (from 6.9 ± 5.6 to 5.6 ± 4.4 mmHg, $p < .01$), ARV (from 8.6 ± 7.7 to 6.9 ± 5.7 mmHg, $p < .05$), and MMD (from 13.2 ± 10.7 to 10.7 ± 8.3 mmHg, $p < .01$) of MHSBP at 12 months; the reduction in these MHSBP variability parameters was comparable to that in adults <70 years. These results suggest that the SPC of Cil/Val is effective in reducing day-by-day variability of MHSBP in elderly patients.

## 1 | INTRODUCTION

Recent hypertension management guidelines recommend the use of fixed-dose single-pill combinations (SPCs) to achieve lower blood pressure (BP) levels.[1–4] In particular, the hypertension guidelines of the European Society of Cardiology and European Society of Hypertension recommend that a fixed-dose SPC is initiated as first-line treatment.[5]

We have previously reported that the SPC of cilnidipine (10 mg) and valsartan (80 mg) (SPC of Cil/Val) is useful to reduce home BP in patients with uncontrolled hypertension with sympathetic hyperactivity.[6] Cil, a component of the SPC of Cil/Val and unique

L-/N-type calcium channel blocker, directly dilates vascular vessels by blocking L-type calcium channels[7] and suppresses elevated sympathetic activity in animal models[8] and patients with hypertension[9] by blocking N-type calcium channels.[10] Sympathetic hyperactivity is reported to be a cause of BP variability.[11,12] Therefore, we tested whether the SPC of Cil/Val could reduce BP variability in patients with hypertension.

In this sub-analysis report, we describe the first study to evaluate the efficacy of the SPC of Cil/Val on the day-by-day variability of morning home systolic BP (MHSBP) in patients with treated hypertension in real-world settings.

## 2 | METHODS

### 2.1 | Study design and population

The protocol of this multicenter, post-marketing, prospective observational survey, home BP control by a single-pill combination of cilnidipine and valsartan (HOPE-Combi), has already been described in previous reports.[6,13] HOPE-Combi was approved by the Ministry of Health, Labour and Welfare of the Japanese Government and conducted in accordance with the Japanese Good Post-marketing Study Practice guidelines. In compliance with the Japanese regulations for post-marketing surveillance, the need for informed consent was waived. This survey was also conducted with the approval of the respective institutional review board or ethics committee of each participating medical institution, if needed, and registered as a post-marketing survey in the University Hospital Medical Information Network (UMIN000037536). All patients received instructions; measurement should be performed twice per occasion, within 1 h after waking up, after urination, before dosing in the morning, before breakfast, and after 1-2-min resting in a sitting position, from the physicians regarding the measurement of home BP,[14,15] as recommended by the guidelines of the Japanese Society of Hypertension for self-monitoring of BP at home.[16] Each patient used an electronic cuff oscillometric device approved by the Ministry of Health, Labour and Welfare of Japan and recorded home BP in a notebook specialized for home BP management. In this sub-analysis, we selected 616 from 2575 patients with a safety assessment of the SPC of Cil/Val.[13] The selection criteria were as follows: 1. had 3 days of MHSBP values at the baseline and 2. had been pretreated with antihypertensive drugs at the baseline. The SPC of Cil/Val was administrated once a day in the morning.

### 2.2 | Statistical analysis

Data are expressed as mean ± standard deviation (SD) or as a percentage for discrete variables. The average values of MHSBP were used for data analysis in the patients whose collection date was 3 days. The SD, coefficient of variation (CV), average real variability (ARV), and the difference between maximum and minimum (MMD) of MHSBP were calculated.[17,18] Changes in MHSBP, SD, CV, ARV, and MMD at 3 and 12 months were analyzed using Dunnett's multiple comparison test. Differences in MHSBP or BP variability were analyzed using the *t*-test. The age-related trends of MHSBP and BP variabilities were analyzed using ANOVA. A $p$ value <.05 was considered statistically significant. All statistical analyses were computed using a statistical software package (SAS, version 9.3, SAS Institute) in an independent facility (INTAGE Healthcare Inc.).

## 3 | RESULTS

### 3.1 | Patient characteristics

Among all 616 patients, 53.2% were men and the average age was 67.0 ± 11.7 years. The comorbid disease percentage was 77.8% (ischemic heart disease, 9.4%; cerebral vascular disease, 6.3%; chronic kidney disease, 12.5%; and hyperuricemia, 12.8%). All patients were pretreated with antihypertensive drugs; the percentage of patients who received a calcium channel blocker was 71.1%. Concomitant antihypertensive drugs were administered to 195 patients (31.7%).

### 3.2 | Age-related trends in MHSBP and BP variabilities at the baseline

MHSBP did not change at all ages ($p$ = .59). The variability of MHSBP increased with age; however, BP variability was not increased in patients ≥70 years and the relationship between age and BP variability was sigmoidal (Figure 1).

### 3.3 | Changes in MHSBP and BP variabilities

At 3 months, MHSBP decreased from 146.4 ± 14.9 ($N$ = 616) to 135.5 ± 12.6 mmHg ($N$ = 525, $p$ < .01), SD decreased from 6.3 ± 4.8 ($N$ = 616) to 5.3 ± 3.9 mmHg ($N$ = 525, $p$ < .01), CV did not decrease significantly (from 4.3 ± 3.2 [$N$ = 616] to 4.0 ± 2.9% [$N$ = 525, $p$ = .11]), ARV decreased from 7.9 ± 6.6 ($N$ = 616) to 6.7 ± 5.4 mmHg ($N$ = 525, $p$ < .01), and MMD decreased from 11.9 ± 9.2 ($N$ = 616) to 10.2 ± 7.5 mmHg ($N$ = 525, $p$ < .01); however, at 12 months, MHSBP decreased to 133.2 ± 10.4 mmHg ($N$ = 445, $p$ < .01), SD decreased to 5.1 ± 3.8 mmHg ($N$ = 445, $p$ < .01), CV decreased to 3.8 ± 2.9% ($N$ = 445, $p$ < .05), ARV decreased to 6.3 ± 5.1 mmHg ($N$ = 445, $p$ < .01), and MMD decreased to 9.7 ± 7.2 mmHg ($N$ = 445, $p$ < .01). Either the pretreatment or concomitant antihypertensive drugs did not affect the lowering action of SPC of Cil/Val against MHSBP and SD (Table S1-S4).

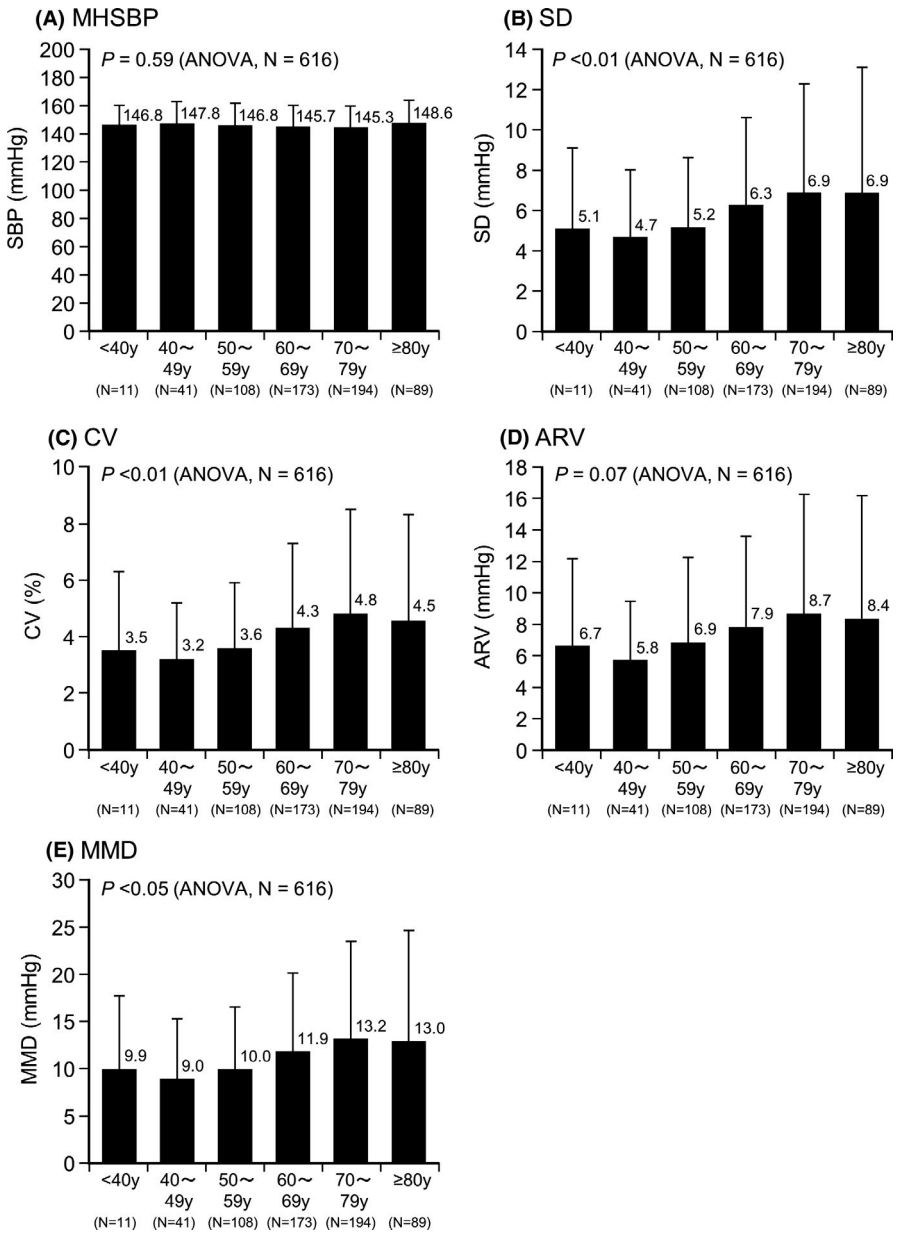


**FIGURE 1** Age-related trends in morning home systolic blood pressure and BP variabilities. Abbreviations: ARV, average real variability; CV, coefficient of variation; MHSBP, morning home systolic blood pressure; MMD, the difference between maximum and minimum; SD, standard deviation; y, years. Data are presented as mean ± SD. The numbers in parentheses indicate the number of subjects

### 3.4 | Changes in MHSBP and BP variabilities at 3 and 12 months in patients aged ≥70 or <70 years

Because BP variability was not increased in patients ≥70 years, we divided patients into two groups according to their age ≥70 or <70 years. At the baseline, MHSBP was not different between patients aged ≥70 years ($N$ = 283) and <70 years ($N$ = 333, $p$ = 1.00); however, the SD ($P$ < .01), CV ($p$ < .01), ARV ($p$ < .05), and MMD ($p$ < .01) were higher in ≥70 year-old patients than in < 70-year-old patients. MHSBP decreased at 3 months and 12 months in both the ≥70 and <70 age groups, and there was no difference in the changes in MHSBP at 3 months and 12 months between patients aged ≥70 and <70 years. The SD, ARV, and MMD decreased in patients aged <70 years and ≥70 years at both 3 months and 12 months. There was no difference in the changes in SD, ARV, and MMD between the ≥70 and <70 age groups at 3 months and 12 months. The CV did not decrease in patients aged ≥70 years and <70 years at 3 months and 12 months (Table 1).

## 4 | DISCUSSION

This study demonstrates that an SPC of Cil, a unique L-/N-type calcium channel blocker,[19] and Val decreased the variability of MHSBP in patients with treated hypertension, regardless of age. The SPC of Cil/Val decreased the day-by-day BP variability parameters of MHSBP, such as SD, CV, ARV, and MMD, at 12 months in 616 patients with treated hypertension.

Hypertension in older adults is reported as a risk factor for atherosclerosis, and also aging with hypertension may lead to cardiovascular events.[20] Therefore, we evaluated the variability of BP in elderly treated hypertensive patients in this survey. The variability

**TABLE 1** Morning home systolic blood pressure and parameters of blood pressure variability at the baseline and 3 and 12 months after the SPC of Cil/Val treatment by age at baseline

| | Age | Baseline | N | *P* valve (t-test) | 3 months | N | *P* value (Dunnett's test) | Changes | *P* valve (t-test) | 12 months | N | *P* value (Dunnett's | Changes | *P* valve (t-test) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MHSBP (mmHg) | <70 years | 146.4 ± 15.0 | 333 | 1.00 | 135.3 ± 12.0 | 290 | <.01 | −11.6 ± 13.8 | .33 | 132.8 ± 10.0 | 243 | <.01 | −13.7 ± 16.2 | .66 |
| | ≥70 years | 146.4 ± 14.9 | 283 | | 135.8 ± 13.2 | 235 | <.01 | −10.4 ± 15.2 | | 133.7 ± 11.0 | 202 | <.01 | −13.1 ± 14.9 | |
| SD (mmHg) | <70 years | 5.7 ± 3.9 | 333 | <.01 | 5.0 ± 3.5 | 290 | <.05 | −0.62 ± 4.30 | .23 | 4.7 ± 3.1 | 243 | <.01 | −0.80 ± 4.38 | .35 |
| | ≥70 years | 6.9 ± 5.6 | 283 | | 5.7 ± 4.4 | 235 | <.01 | −1.14 ± 5.67 | | 5.6 ± 4.4 | 202 | <.01 | −1.26 ± 5.73 | |
| CV (%) | <70 years | 3.9 ± 2.7 | 333 | <.01 | 3.7 ± 2.6 | 290 | .60 | −0.10 ± 3.07 | .24 | 3.5 ± 2.4 | 243 | .15 | −0.19 ± 3.13 | .42 |
| | ≥70 years | 4.7 ± 3.7 | 283 | | 4.2 ± 3.2 | 235 | .17 | −0.47 ± 4.05 | | 4.2 ± 3.3 | 202 | .19 | −0.46 ± 4.01 | |
| ARV (mmHg) | <70 years | 7.3 ± 5.4 | 333 | <.05 | 6.3 ± 4.7 | 290 | <.05 | −0.93 ± 6.28 | .54 | 5.9 ± 4.4 | 243 | <.01 | −1.20 ± 6.42 | .50 |
| | ≥70 y | 8.6 ± 7.7 | 283 | | 7.1 ± 6.1 | 235 | <.05 | −1.32 ± 8.09 | | 6.9 ± 5.7 | 202 | <.05 | −1.65 ± 7.99 | |
| MMD (mmHg) | <70 y | 10.9 ± 7.5 | 333 | <.01 | 9.6 ± 6.7 | 290 | <.05 | −1.14 ± 8.25 | .26 | 8.9 ± 6.0 | 243 | <.01 | −1.51 ± 8.36 | .36 |
| | ≥70 y | 13.2 ± 10.7 | 283 | | 10.9 ± 8.4 | 235 | <.05 | −2.09 ± 10.88 | | 10.7 ± 8.3 | 202 | <.01 | −2.35 ± 11.00 | |

*Note*: Data are presented as mean ± SD.

MHSBP, morning home systolic blood pressure; SD, standard deviation; CV, coefficient of variation; ARV, average real variability; MMD, the difference between maximum and minimum; y, years.

of MHSBP increased in an age-dependent manner but not in patients aged ≥70 years at the baseline. In 333 patients aged ≥70 years with treated hypertension, the SPC of Cil/Val decreased the variability of MHSBP and the degrees of change of the variability of MHSBP were not different from those in 283 patients aged <70 years. These results suggest that the SPC of Cil/Val was effective in the reduction of BP variability in elderly patients with treated hypertension. In this study, at the baseline, the MHSBP was constant at all ages, whereas the day-by-day variability of MHSBP increased with age in patients with hypertension administered antihypertensive drugs. In the general population of Ohasama, both home BP and day-by-day BP variability increase with age.[21] The home BP variability is a risk factor for the development of cardiovascular events, independent of the average home BP,[22–24] and is associated with renal function.[25] In elderly hypertensive patients, the BP variability is also reported as a risk factor for mortality[26,27] and cardiovascular death[28] and a predictor of arterial stiffness progression.[29] Our conclusion that the SPC of Cil/Val reduces age-related increased home BP variability may have clinical significance. This benefit needs to be confirmed in the future.

Sympathetic nervous hyperactivity leads to an increase in BP variability.[30,31] Cil, a component of the SPC of Cil/Val, suppresses elevated sympathetic activity in patients with hypertension.[9] This sympatholytic activity of Cil may contribute to the decrease in the day-by-day variability of MHSBP. Increased arterial stiffness also leads to high BP variability [32] and the SPC of Cil/Val ameliorates arterial stiffness in patients with hypertension.[6] This action may also contribute to the decrease in BP variability at 12 months.

## 5 | STUDY LIMITATIONS

In this real-world survey, missing data might have affected the results and no control group was used. Therefore, a relative evaluation of the efficacy of the SPC of Cil/Val was not possible and the effect of the SPC of Cil/Val for the variability of morning home systolic blood pressure may involve a consequence of the regression to the mean. Self-measured home BP data were recorded by patients in a notebook and handed to practitioners. Therefore, data may potentially include transcription errors.

## 6 | CONCLUSIONS

In conclusion, the sub-analysis of the HOPE-Combi survey results has shown that the SPC of Cil/Val was effective in the reduction of exaggerated day-by-day variabilities of MHSBP in elderly patients with treated hypertension in a real-world setting.

### ACKNOWLEDGEMENTS

We would like to express our deepest gratitude to the physicians who provided valuable data and for their cooperation in conducting the study.

## CONFLICT OF INTERESTS

Kazuomi Kario received scholarship donations from Mochida Pharmaceutical Co., Ltd., and an honorarium as a medical professional from EA Pharma Co., Ltd., for this survey. Saori Matsuda, Shinobu Nagahama, and Yoshiki Kurose are employees of EA Pharma Co., Ltd. Hitoshi Sugii, Tsukasa Teshima, and Noriyuki Suzuki are employees of Mochida Pharmaceutical Co., Ltd.

## ORCID

*Kazuomi Kario* https://orcid.org/0000-0002-8251-4480

## REFERENCES


1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):e13-e115.
2. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*. 2020;75(6):1334-1357.
3. Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. Hypertension Canada's 2020 Comprehensive guidelines for the prevention, diagnosis, risk assessment, and treatment of hypertension in adults and children. *Can J Cardiol*. 2020;36(5):596-624. https://doi.org/10.1016/j.cjca.2020.02.086
4. Umemura S, Arima H, Arima S, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019). *Hypertens Res*. 2019;42(9):1235-1481. https://doi.org/10.1038/s41440-019-0284-9
5. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021-3104. https://doi.org/10.1093/eurheartj/ehy339
6. Kario K, Matsuda S, Nagahama S, et al. Single-pill combination of cilnidipine, an L-/N-type calcium channel blocker, and valsartan effectively reduces home pulse pressure in patients with uncontrolled hypertension and sympathetic hyperactivity: The HOPE-Combi survey. *J Clin Hypertens (Greenwich)*. 2020;22(3):457-464. https://doi.org/10.1111/jch.13771
7. Leung HS, Yao X, Leung FP, et al. Cilnidipine, a slow-acting Ca2+ channel blocker, induces relaxation in porcine coronary artery: role of endothelial nitric oxide and [Ca2+]i. *Br J Pharmacol*. 2006;147(1):55-63. https://doi.org/10.1038/sj.bjp.0706450
8. Takahara A, Koganei H, Takeda T, Iwata S. Antisympathetic and hemodynamic property of a dual L/N-type Ca(2+) channel blocker cilnidipine in rats. *Eur J Pharmacol*. 2002;434(1–2):43-47. https://doi.org/10.1016/s0014-2999(01)01521-7
9. Sakata K, Shirotani M, Yoshida H, et al. Effects of amlodipine and cilnidipine on cardiac sympathetic nervous system and neurohormonal status in essential hypertension. *Hypertension*. 1999;33(6):1447-1452.
10. Uneyama H, Takahara A, Dohmoto H, Yoshimoto R, Inoue K, Akaike N. Blockade of N-type Ca2+ current by cilnidipine (FRC-8653) in acutely dissociated rat sympathetic neurones. *Br J Pharmacol*. 1997;122(1):37-42. https://doi.org/10.1038/sj.bjp.0701342
11. Mancia G, Di Rienzo M, Parati G, Grassi G. Sympathetic activity, blood pressure variability and end organ damage in hypertension. *J Hum Hypertens*. 1997;11(Suppl 1):S3-S8.
12. Zuern CS, Rizas KD, Eick C, et al. Effects of renal sympathetic denervation on 24-hour blood pressure variability. *Front Physiol*. 2012;3:134. https://doi.org/10.3389/fphys.2012.00134
13. Matsuda S, Nagahama S, Kurose Y, et al. A post-marketing survey evaluating the safety and efficacy of a fixed-dose single-pill combination of cilnidipine and valsartan in patients with hypertension: Real-world JSH 2014 and 2019 implementations. *Clin Exp Hypertens*. 2020;42(6):502-511. https://doi.org/10.1080/10641963.2020.1714641
14. Kario K, Park S, Buranakitjaroen P, et al. Guidance on home blood pressure monitoring: a statement of the HOPE Asia Network. *J Clin Hypertens (Greenwich)*. 2018;20(3):456-461. https://doi.org/10.1111/jch.13216
15. Kario K, Park S, Chia YC, et al. 2020 Consensus summary on the management of hypertension in Asia from the HOPE Asia Network. *J Clin Hypertens (Greenwich)*. 2020;22(3):351-362. https://doi.org/10.1111/jch.13751
16. Imai Y, Kario K, Shimada K, et al. The Japanese Society of Hypertension Guidelines for Self-monitoring of Blood Pressure at Home (Second Edition). *Hypertens Res*. 2012;35(8):777-795. https://doi.org/10.1038/hr.2012.56
17. Asayama K, Kikuya M, Schutte R, et al. Home blood pressure variability as cardiovascular risk factor in the population of Ohasama. *Hypertension*. 2013;61(1):61-69. https://doi.org/10.1161/HYPERTENSIONAHA.111.00138
18. Juhanoja EP, Niiranen TJ, Johansson JK, et al. Outcome-driven thresholds for increased home blood pressure variability. *Hypertension*. 2017;69(4):599–607
19. Takahara A. Cilnidipine: a new generation Ca channel blocker with inhibitory action on sympathetic neurotransmitter release. *Cardiovasc Ther*. 2009;27(2):124-139. https://doi.org/10.1111/j.1755-5922.2009.00079.x
20. Spannella F, Di Pentima C, Giulietti F, et al. Prevalence of subclinical carotid atherosclerosis and role of cardiovascular risk factors in older adults: atherosclerosis and aging are not synonyms. *High Blood Press Cardiovasc Prev*. 2020;27(3):231-238. https://doi.org/10.1007/s40292-020-00375-0
21. Satoh M, Metoki H, Asayama K, et al. Age-related trends in home blood pressure, home pulse rate, and day-to-day blood pressure and pulse rate variability based on longitudinal cohort data: The Ohasama Study. *Journal of the American Heart Association*. 2019;8(15):e012121. https://doi.org/10.1161/JAHA.119.012121
22. Kikuya M, Ohkubo T, Metoki H, et al. Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis. *Hypertension*. 2008;52(6):1045-1050. https://doi.org/10.1161/HYPERTENSIONAHA.107.104620
23. Hoshide S, Yano Y, Mizuno H, Kanegae H, Kario K. Day-by-day variability of home blood pressure and incident cardiovascular disease in clinical practice. *Hypertension*. 2018;71(1):177-184. https://doi.org/10.1161/HYPERTENSIONAHA.117.10385
24. Parati G, Torlasco C, Pengo M, Bilo G, Ochoa JE. Blood pressure variability: its relevance for cardiovascular homeostasis and cardiovascular diseases. *Hypertens Res*. 2020;43(7):609-620. https://doi.org/10.1038/s41440-020-0421-5
25. Suzuki D, Hoshide S, Kario K. Associations between day-by-day home blood pressure variability and renal function and albuminuria in patients with and without diabetes. *Am J Hypertens*. 2020;33(9):860–868. https://doi.org/10.1093/ajh/hpaa091
26. Chowdhury EK, Wing LMH, Jennings GLR, Beilin LJ, Reid CM. Visit-to-visit (long-term) and ambulatory (short-term) blood pressure variability to predict mortality in an elderly hypertensive population. *J Hypertens*. 2018;36(5):1059-1067. https://doi.org/10.1097/hjh.0000000000001652
27. Chowdhury EK, Nelson MR, Wing LMH, et al. Change in blood pressure variability among treated elderly hypertensive patients and its association with mortality. *J Am Heart Assoc*. 2019;8(21):e012630. https://doi.org/10.1161/JAHA.119.012630
28. Kostis JB, Sedjro JE, Cabrera J, et al. Visit-to-visit blood pressure variability and cardiovascular death in the Systolic Hypertension in

the Elderly Program. *J Clin Hypertens (Greenwich)*. 2014;16(1):34-40. https://doi.org/10.1111/jch.12230
29. Nagai M, Dote K, Kato M, et al. Visit-to-visit blood pressure variability, average BP level and carotid arterial stiffness in the elderly: a prospective study. *J Hum Hypertens*. 2017;31(4):292-298. https://doi.org/10.1038/jhh.2016.77
30. Coulson JM. The relationship between blood pressure variability and catecholamine metabolites: a pilot study. *J Hum Hypertens*. 2015;29(1):50-52. https://doi.org/10.1038/jhh.2014.23
31. Hintsala HE, Kiviniemi AM, Antikainen R, et al. High home blood pressure variability associates with exaggerated blood pressure response to cold stress. *Am J Hypertens*. 2019;32(6):538-546. https://doi.org/10.1093/ajh/hpz011
32. Ishiyama Y, Hoshide S, Kanegae H, Kario K. Increased arterial stiffness amplifies the association between home blood pressure variability and cardiac overload. *Hypertension*. 2020;75(6):1600–1606. https://doi.org/10.1161/HYPERTENSIONAHA.119.14246

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Kario K, Matsuda S, Nagahama S, et al. Single-pill combination of cilnidipine, an l-/n-type calcium channel blocker, and valsartan reduces the day-by-day variability of morning home systolic blood pressure in patients with treated hypertension: A sub-analysis of the HOPE-combi survey. *J Clin Hypertens*. 2021;23:392–397. https://doi.org/10.1111/jch.14178