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, PhD1 | Saori Matsuda BSc2 | Shinobu Nagahama BSc2 | Yoshiki Kurose BSc2 | Hitoshi Sugii BSc3 | Tsukasa Teshima BA3 | Noriyuki Suzuki BSc4

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...
2 | METHODS

2.1 | Study design and population

The protocol of this multicenter, post-marketing, prospec- tive observational study, 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 measurement should be performed twice per occasion, within 1 h after 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 per- centage 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 mul- tiple 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 per- centage 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 de- crease 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).
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, 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. Therefore, we evaluated the variability of BP in elderly treated hypertensive patients in this survey. The variability...
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. We would like to express our deepest gratitude to the physicians who provided valuable data and for their cooperation in conducting the study.

STUDY LIMITATIONS

In this real-world setting, 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 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.

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. The benefit needs to be confirmed in the future.

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.

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 value (t-test) | Changes | P value (Dunnett's test) | N  | Changes | P value (Dunnett's test) | Changes |
|-------------|----------|----|-----------------|---------|--------------------------|----|---------|--------------------------|---------|
| 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 | <.01 | 135.8 ± 13.2 | 235 | <.01 | -10.4 ± 15.2 | .01 | 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 | <.01 | 5.7 ± 4.4   | 235 | <.01 | -1.14 ± 5.67 | .02 | 5.6 ± 4.4   | 202 | <.01 | -1.26 ± 5.73 |
| CV (%)      | <70 years| 3.9 ± 2.7   | 333 | <.01 | 3.7 ± 2.6   | 290 | <.05 | -0.10 ± 3.07 | .24 | 3.5 ± 2.4   | 243 | <.01 | -0.19 ± 3.13 | .42 |
|             | ≥70 years| 4.7 ± 3.7   | 283 | <.01 | 4.2 ± 3.2   | 235 | <.01 | -0.47 ± 4.05 | .02 | 4.3 ± 3.3   | 202 | <.01 | -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 years| 8.6 ± 7.7   | 283 | <.05 | 7.1 ± 6.1   | 235 | <.05 | -1.32 ± 8.09 | .02 | 6.9 ± 5.7   | 202 | <.05 | -1.65 ± 7.99 |
| MMD (mmHg)  | <70 years| 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 years| 13.2 ± 10.7 | 283 | <.01 | 10.9 ± 8.4  | 235 | <.05 | -2.09 ± 10.88| .02 | 10.7 ± 8.3  | 202 | <.01 | -2.35 ± 11.00|
REFERENCES

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/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/10.1083/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/10.1016/j.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. Antisymptathic and hemodynamic property of a dual L-N-type Ca2+ 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 neurohumoral 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):S3-58.

12. Zuehn 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/HYPTENSIONA111.00138

18. Juhanonja 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. Sato 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, Bilò G, Ochon J.E. Blood pressure variability: its relevance for cardiovascular homeostasis and cardiovascular diseases. Hypertens Res. 2020;43(7):609-620. https://doi.org/10.1007/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

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
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