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ORIGINAL ARTICLE

Effects of calcium channel blocker-based combinations on intra-individual blood pressure variability: *post hoc* analysis of the COPE trial

Seiji Umemoto[1], Toshio Ogihara[2,3], Masunori Matsuzaki[4], Hiromi Rakugi[3], Yasuo Ohashi[5], Takao Saruta[6] and the Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) Trial Group

Visit-to-visit blood pressure (BP) variability is an important predictor of stroke. However, which antihypertensive drug combination is better at reducing visit-to-visit BP variability and therefore at reducing stroke incidence remains uncertain. We have previously reported that the dihydropyridine calcium channel blocker benidipine combined with a β-blocker appeared to be less beneficial in reducing the risk of stroke than a combination of benidipine and thiazide. Here, we further compare the visit-to-visit BP variability among three benidipine-based regimens, namely angiotensin receptor blocker (ARB), β-blocker and thiazide combinations. The present *post hoc* analysis included 2983 patients without cardiovascular events or death during the first 18 months after randomization. We compared the BP variability (defined as the s.d. and the coefficient of variation (CV)), maximum systolic BP (SBP) and diastolic BP (DBP) of the clinic mean on-treatment BPs obtained at 6-month intervals, starting 6 months after the treatment initiation, among the 3 treatments (ARB, $n=1026$; β-blocker, $n=966$; thiazide, $n=991$). During the first 6–36 months after randomization, both the s.d. and CV-BPs were lower in the benidipine–thiazide group than in the benidipine–β-blocker group (s.d.-SBP, $P=0.019$; s.d.-DBP, $P=0.030$; CV-SBP, $P=0.012$; CV-DBP, $P=0.022$). The s.d. and CV in the ARB group did not reach statistical significance compared with the other two groups. The maximum BPs did not differ among the three treatments. These findings suggest that the benidipine–thiazide combination may reduce visit-to-visit BP variability more than the benidipine–β-blocker combination.
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Keywords: calcium channel blockers; drug combination therapy; intra-individual blood pressure variability; thiazide; β-blocker

INTRODUCTION

The Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) trial was the first clinical trial to examine the treatment of hypertension with combination therapies including benidipine, a potent and long-acting dihydropyridine calcium channel blocker (CCB), which inhibits not only L-type and N-type calcium channels but also T-type calcium channels.[1] In this trial, although the percentages of subjects achieving the target blood pressure (BP; $<140/90$ mm Hg) and the incidences of primary composite cardiovascular endpoints, including the reduction in BP, from baseline over the course of the trial were similar among the benidipine–thiazide diuretic (thiazide), benidipine–angiotensin receptor blocker (ARB) and benidipine–β-blocker groups, secondary analyses suggested that, especially in elderly subjects, benidipine combined with a β-blocker appeared to be less beneficial in reducing the risk of both hemorrhagic and ischemic stroke compared with the benidipine–thiazide combination.[2–5]

Although the adverse cardiovascular consequences of hypertension largely depend on the absolute BP values,[6] the targeting of antihypertensive treatment towards stabilizing long-term BP variability has also been suggested.[7,8] Moreover, it is important to note that the effects on inter-individual BP variation may account for the differences in the effects of antihypertensive drugs on the risk of stroke, independently of their effects on the mean systolic BP (SBP).[9,10] Furthermore, it has been reported that the effects of antihypertensive drugs on SBP variability are dose dependent and persist when used in combinations, and that the use of a high dose of a CCB alone or in combination with other agents is likely to be particularly effective in preventing stroke.[11] However, the inter-patient dispersion of the mean BP during treatment reflects the different effect of the BP-lowering treatment in a group of patients and does not quantify visit-to-visit BP variability in individual patients. By contrast, a reduction of intra-individual BP variability[12] may have a role in improving patient outcomes, as demonstrated in a previous clinical trial.[13] Thus, to

[1]Center for Clinical Research, Yamaguchi University Hospital, Yamaguchi, Japan; [2]Morinomiya University of Medical Sciences, Osaka, Japan; [3]Department of Geriatric Medicine and Nephrology, Osaka University Graduate School of Medicine, Osaka, Japan; [4]Yamaguchi University, Yamaguchi, Japan; [5]Department of Integrated Science and Engineering for Sustainable Society, Faculty of Science and Engineering, Chuo University, Tokyo, Japan and [6]Keio University, Tokyo, Japan
Correspondence: Dr S Umemoto, Center for Clinical Research, Yamaguchi University Hospital, 1-1-1 Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan.
E-mail: umemoto@yamaguchi-u.ac.jp
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clarify which antihypertensive drug combination is better at reducing visit-to-visit BP variability, we utilized a *post hoc* analysis to compare the intra-individual visit-to-visit BP variability among the three benidipine-based regimens evaluated in the COPE trial.

METHODS

Study design of the *post hoc* analysis of the COPE trial

The COPE trial was an investigator-initiated multi-center study with a prospective, randomized, open-label, blinded-endpoint (PROBE) design that compared the cardiovascular effects and achievement of target BP (<140/90 mm Hg) between 3 dihydropyridine CCB benidipine-based regimens (ARB, β-blocker or thiazide) in 3501 hypertensive patients who had not achieved the target BP with benidipine alone at a dose of 4 mg per day. The BP management titration algorithm, together with other details of the study design and the results of the COPE trial, have already been reported.[2–4] In brief, participants aged 40–85 years with a sitting SBP ⩾140 mm Hg and/or a diastolic BP (DBP) ⩾90 mm Hg, whether untreated or treated, who did not achieve the target BP in the sitting position at our clinic following monotherapy with benidipine at a dose of 4 mg per day during the run-in phase (4–8 weeks) were included in the study. These patients were randomly assigned to receive benidipine combined with an ARB, a β-blocker or a thiazide. After randomization, all of the patients were followed every 6 months for at least 36 months (BP measurement phase). At each visit, BP measurements were performed by trained physicians according to the guidelines for the management of hypertension;[14] the clinic BP was standardized and measured by the auscultation method using mercury or an automatic sphygmomanometer that was calibrated once a year throughout the BP measurement phase. The BP was measured at randomization (baseline), at monthly intervals to achieve the target BP after randomization (drug titration phase) and every 6 months thereafter. At each visit, the BP was measured two or more times at intervals of 1 to 2 min, and the mean of two stable measurements (difference <5 mm Hg) was used as the representative value for each visit and was regarded as the patient's clinic BP.

A total of 3293 patients who were prescribed a combination treatment (ARB, $n=1110$; β-blocker, $n=1089$; thiazide, $n=1094$) were compared using full set analysis to specifically evaluate the effects of benidipine-based combination therapy for hypertension in the COPE trial.[3] Of these, 2983 patients (ARB, $n=1026$; β-blocker, $n=966$; thiazide, $n=991$) met the following inclusion criteria and were included in this *post hoc* analysis (Figure 1): (1) subjects who did not develop any cardiovascular events within 18 months after randomization, and (2) subjects who had their clinic BP measured at least three times over a BP measurement phase of at least 18 months to evaluate intra-individual visit-to-visit BP variability during the 36-month BP measurement phase.

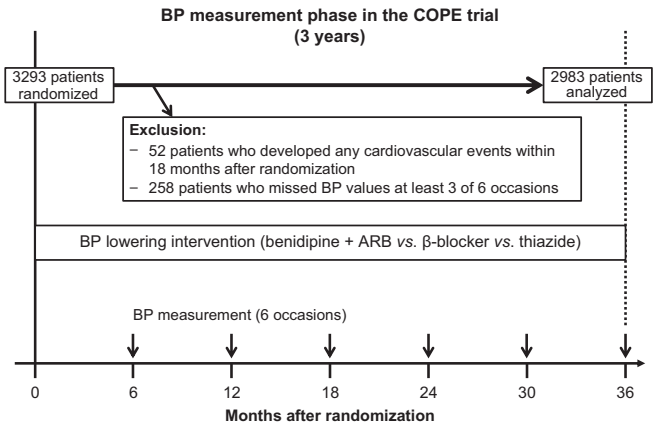

Figure 1 Flow diagram of the study participants. The blood pressure was measured at six time points (6, 12, 18, 24, 30, and 36 months after randomization) and was used to determine the mean, maximum and minimum, and intra-individual visit-to-visit variability of systolic and diastolic BPs. After excluding patients who had experienced any cardiovascular events within 18 months after randomization and patients with missing BP values from 3 or more of the 6 time points, 2983 patients were eligible for enrollment in the present study. ARB, angiotensin receptor blocker; BP, blood pressure; COPE, Combination Therapy of Hypertension to Prevent Cardiovascular Events.

Data analysis

For each patient, the mean SBP and DBP values measured at each visit during the 36-month BP measurement phase and the maximum and minimum SBP and DBP values were selected for analysis. In addition to the s.d. and the coefficient of variation (CV) of the mean BP, the long-term intra-individual variability in SBP and DBP were analyzed separately for the three treatment groups. For clinic BP in each patient, only the BP values obtained during the first 6-month visit and onward were considered, and the BP changes occurring during the drug titration phase were therefore not included in the calculation. BP recordings were performed at registration, at randomization, at 3, 4 and 6 months after randomization, and every 6 months thereafter. The mean of the two stable measurements taken at each visit was used as the BP value for that visit. The BP values measured at six occasions (6, 12, 18, 24, 30 and 36 months after randomization) were used to determine the mean BP, visit-to-visit variability, and the maximum and minimum SBP and DBP, as well as the difference between the maximum and minimum (maximum–minimum) values. After excluding patients who had experienced primary cardiovascular events and patients with missing BP values for 3 or more of the 6 occasions, 2983 patients were eligible for the present study (Figure 1). For each patient, the s.d. was divided by the corresponding mean on-treatment BP value to express the intra-individual visit-to-visit variability as a CV or, in other words, as a normalized value. The individual values were averaged to obtain mean values for each group considered.

Statistics

Throughout the text, group values are expressed as the mean ± s.d. or a percentage. Continuous variables among the three treatment groups were compared using one-way analysis of variance, as appropriate. Categorical variables among the three treatment groups were compared with the χ^2-test. Differences in the mean, maximum, minimum, maximum–minimum, s.d., and CV of the BP values and in the number of clinic BP measurements in the three treatment groups during the 36-month BP measurement phase were analyzed using Tukey's multiple comparison test. Only BP values obtained before a cardiovascular event were used to calculate the visit-to-visit BP variability. All data were analyzed using SAS System Release 9.1 (SAS Institute, Cary, NC, USA). All *P*-values were two sided, and a value of $P<0.05$ was considered statistically significant.

RESULTS

Demographic and baseline patient characteristics of the *post hoc* analysis of the COPE trial

Demographic and baseline characteristics, including the baseline SBP and DBP, the previous history of cardiovascular disease and the need for anti-platelet therapy were well-matched among the patients randomized to the three regimens in this *post hoc* analysis of the COPE trial (Table 1).

Number of visits and BP control during the treatment

Over 85% of the subjects in each group had their clinic BP measured on six occasions, and the number of BP measurements did not significantly differ from those of the other two treatment regimens when grouped together (Supplementary Table S1).

The reduction in SBP and DBP from baseline was similar among the three treatment groups over the course of the trial (Supplementary Figure S1). There were no differences among the three treatment groups in the mean BP after 36 months of treatment. At the end of the treatment phase, the mean BP was 134.8/77.2 mm Hg in the benidipine–ARB group, 133.9/77.0 mm Hg in the benidipine–β-blocker group and 134.0/76.6 mm Hg in the benidipine–thiazide

Table 1 Demographic and baseline characteristics of the study participants

	Benidipine plus ARB (n = *1026*)	*Benidipine plus BB* (n = *966*)	*Benidipine plus TD* (n = *991*)	P-*value*
Demographic				
Sex, male	520 (50.7%)	480 (49.7%)	495 (49.9%)	0.899
Age, years	63.0 ± 10.6	63.3 ± 10.7	63.5 ± 10.6	0.594
Baseline characteristics				
BMI, kg m^{-2}	24.7 ± 3.4	24.6 ± 3.4	24.4 ± 3.4	0.209
Systolic BP, mm Hg	153.8 ± 11.8	153.6 ± 10.7	154.2 ± 12.0	0.491
Diastolic BP, mm Hg	89.0 ± 9.7	88.5 ± 9.6	88.5 ± 9.8	0.362
Heart rate, beats per min	74.0 ± 11.1	74.3 ± 11.0	74.2 ± 11.5	0.865
Risk factors				
Previous cardiovascular disease	131 (12.8%)	110 (11.4%)	129 (13.0%)	0.500
Previous stroke	31 (3.0%)	23 (2.4%)	23 (2.3%)	0.546
Diabetes	144 (14.0%)	137 (14.2%)	143 (14.4%)	0.968
Dyslipidemia	400 (39.0%)	391 (40.5%)	418 (42.2%)	0.344
Current smoking	399 (38.9%)	376 (38.9%)	390 (39.4%)	0.972
Previous medication				
Antihypertensive agents	824 (80.3%)	780 (80.7%)	803 (81.0%)	0.919
Benidipine	647 (63.1%)	620 (64.2%)	632 (63.8%)	0.870
Other CCB	120 (11.7%)	109 (11.3%)	113 (11.4%)	0.957
ARB	94 (9.2%)	93 (9.6%)	95 (9.6%)	0.925
ACE inhibitor	17 (1.7%)	22 (2.3%)	13 (1.3%)	0.255
BB	23 (2.2%)	35 (3.6%)	33 (3.3%)	0.165
Diuretics	9 (0.9%)	8 (0.8%)	13 (1.3%)	0.494
Concomitant medication				
Anti-platelet agents	88 (8.6%)	72 (7.5%)	77 (7.8%)	0.631
Statin	174 (17.0%)	170 (17.6%)	159 (16.0%)	0.653
Antidiabetic agents	71 (6.9%)	68 (7.0%)	72 (7.3%)	0.954

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, β-blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; TD, thiazide diuretic.
Data are shown as the number of patients (%) or the mean ± s.d. Differences in the proportions among the three treatment groups were analyzed using the χ^2-test, and differences in the means among the three treatment groups were analyzed using one-way analysis of variance.

group. Moreover, the percentage of patients who achieved the target BP did not differ among the three treatment groups over the course of the trial (Supplementary Figure S1). In addition, there were no significant differences seen in the use of concomitant medications at 36 months after study initiation (Supplementary Table S2).

Intra-individual systolic and diastolic variability in BP during the BP measurement phase in the COPE trial

Because very few differences were seen in the SBP and DBP control during the BP measurement phase, as shown in Supplementary Figure S1, we further examined the effects of antihypertensive drug combinations on intra-individual visit-to-visit BP variability during the BP measurement phase in the COPE trial.

Table 2 shows the levels between SBPs and intra-individual visit-to-visit variability in SBP in the three treatment groups during the BP measurement phase. Although the mean, maximum and minimum SBP were not different among the three treatment groups, the difference between the maximum and minimum SBP, as well as the s.d. and CV of SBP, were significantly lower in the benidipine–thiazide group than in the benidipine–β-blocker group. Moreover, although the intra-individual visit-to-visit variability in SBP in the benidipine–ARB group tended to be higher than in the benidipine–thiazide group and lower than in the benidipine–β-blocker group, these indices in the benidipine–ARB regimen during the BP measurement phase did not differ statistically from the benidipine–thiazide or benidipine–β-blocker groups, with the intra-individual visit-to-visit variability in the benidipine–ARB group tending to be closer to that of the benidipine–thiazide group.

Table 3 shows the relationships between the DBP levels and intra-individual visit-to-visit variability in DBP in the 3 treatment groups during the BP measurement phase. Although the mean, maximum, minimum, and the difference between the maximum and minimum DBP did not differ among the 3 treatment groups, not only the DBP but also the s.d. and CV of DBP, were significantly lower in the benidipine–thiazide group than in the benidipine–β-blocker group when analyzed separately. Furthermore, although the intra-individual visit-to-visit variability in the DBP in the benidipine–ARB group tended to be higher than in the benidipine–thiazide group and lower than in the benidipine–β-blocker group, these differences were not significant; however, the intra-individual visit-to-visit variability in the benidipine–ARB group tended to be closer to that of the benidipine–thiazide group.

DISCUSSION

In this *post hoc* analysis of the COPE trial, we demonstrated that intra-individual BP variability, as well as the difference between the maximum and minimum SBP were significantly reduced by benidipine–thiazide combination treatment compared with the benidipine–β-blocker combination, although there were little differences among the three treatment groups in SBP and DBPs throughout the baseline, 36-month treatment and BP measurement phases.

It has been reported that in addition to its vasodilator effects,[1] T/L-type CCB benidipine inhibits aldosterone production,[15] directly inhibits aldosterone-induced mineralocorticoid receptor activation[16,17] and exerts a sodium diuretic action via T-type calcium channel inhibition.[18] In addition, thiazide diuretics initially reduce arterial pressure through a reduction in plasma volume and cardiac output, whereas their long-term pressure reduction effects are mediated through a reduction in the total peripheral resistance.[19] Zhang *et al.*[20] recently investigated the effects of sustained release three antihypertensive drugs, candesartan, amlodipine and indapamide, on BP variability by using ambulatory BP monitoring. They found that only amlodipine- and indapamide-sustained release was associated with significantly decreased BP variability. The reduction in BP variability by amlodipine was found to be significantly associated with reductions in BP and heart rate variability, whereas the corresponding reduction by indapamide-sustained release was only associated with a reduction in heart rate variability at night, suggesting that the mechanisms of these reductions may be attributable to lowering the BP, ameliorating autonomic nervous system regulation or both. These mechanisms may have also affected the results of the present study.

In addition, it has also been reported that both the visit-to-visit variability in SBP and maximum SBP are strong predictors of stroke risk, independent of the mean SBP.[12] In this *post hoc* analysis, a smaller difference between the maximum and minimum SBP, but not the DBP, for the benidipine–thiazide combination compared with the benidipine–β-blocker combination was observed. This suggests that the SBP variability, in addition to the difference between the

Table 2 Systolic blood pressure level and intra-individual visit-to-visit variability in the three treatment groups during the BP measurement phase

				Difference (95% CI)			P-*value*		
	Benidipine plus ARB (n = *1026*)	*Benidipine plus BB* (n = *996*)	*Benidipine plus TD* (n = *991*)	*ARB/BB*	*ARB/TD*	*BB/TD*	*ARB/BB*	*ARB/TD*	*BB/TD*
Mean, mm Hg	135.8 ± 10.2	135.6 ± 10.6	135.5 ± 9.8	0.18 −0.73–1.10	0.24 −0.64–1.12	0.06 −0.85–0.97	0.917	0.859	0.992
Maximum, mm Hg	149.5 ± 14.1	150.2 ± 15.0	149.0 ± 13.9	−0.73 −2.01–0.55	0.52 −0.71–1.74	1.25 −0.04–2.53	0.492	0.698	0.133
Minimum, mm Hg	122.9 ± 11.0	122.5 ± 11.7	122.8 ± 10.9	0.42 −0.58–1.42	0.09 −0.86–1.05	−0.32 −1.33–0.68	0.683	0.981	0.797
Maximum–minimum, mm Hg	26.6 ± 13.3	27.8 ± 14.7	26.2 ± 13.5	1.15 −2.38–0.08	0.42 −0.75–1.59	1.57 0.32–2.82	0.153	0.771	0.032
Visit-to-visit variability									
s.d., mm Hg	10.3 ± 5.2	10.7 ± 5.6	10.1 ± 5.1	−0.43 −0.90–0.05	0.22 −0.23–0.67	0.65 0.17–1.13	0.170	0.618	0.019
CV, %	7.57 ± 3.68	7.90 ± 4.01	7.42 ± 3.64	−0.33 −0.67–0.01	0.16 −0.16–0.48	0.49 0.15–0.83	0.124	0.621	0.012

Abbreviations: ARB, angiotensin receptor blocker; BB, β-blocker; CI, confidence interval; CV, coefficient of variance; TD, thiazide diuretic; s.d., standard deviation.
Data are shown as the mean ± s.d. The following inclusion criteria were adopted for the *post hoc* analysis of the COPE trial: 1) subjects who did not develop any cardiovascular events within 18 months after randomization, and 2) subjects who had measured their clinic BP at least 3 times over at least 18 months to evaluate intra-individual visit-to-visit BP variability during the 36-month BP measurement phase. Differences in the mean, maximum, minimum, maximum–minimum, s.d. and CV of BP values between 2 treatment groups (ARB/BB, ARB/TD, or BB/TD) were analyzed using Tukey's multiple comparison test.

Table 3 Diastolic blood pressure level and intra-individual visit-to-visit variability in the three treatment groups during the BP measurement phase

				Difference (95% CI)			P-*value*		
	Benidipine plus ARB (n = *1026*)	*Benidipine plus BB* (n = *996*)	*Benidipine plus TD* (n = *991*)	*ARB/BB*	*ARB/TD*	*BB/TD*	*ARB/BB*	*ARB/TD*	*BB/TD*
Mean, mm Hg	78.1 ± 7.6	78.0 ± 7.8	78.4 ± 8.0	0.15 −0.53–0.82	−0.30 −0.98–0.38	−0.44 −1.14–0.26	0.909	0.668	0.421
Maximum, mm Hg	87.2 ± 8.9	87.2 ± 9.5	87.2 ± 9.1	−0.07 −0.88–0.74	−0.04 −0.82–0.75	0.03 −0.79–0.86	0.984	0.996	0.996
Minimum, mm Hg	69.3 ± 9.1	69.0 ± 9.2	69.8 ± 9.2	0.26 −0.54–1.07	−0.51 −1.31–0.29	−0.77 −1.59–0.04	0.799	0.424	0.149
Maximum–minimum, mm Hg	17.9 ± 8.5	18.2 ± 8.9	17.4 ± 8.4	0.33 −1.10–0.43	0.47 −0.27–1.22	0.81 0.04–1.57	0.664	0.431	0.096
Visit-to-visit variability									
s.d., mm Hg	6.95 ± 3.23	7.06 ± 3.36	6.70 ± 3.08	−0.11 −0.40–0.18	0.26 −0.02–0.54	0.37 0.08–0.66	0.727	0.167	0.030
CV, %	9.02 ± 4.36	9.18 ± 4.50	8.66 ± 4.14	−0.15 −0.54–0.24	0.37 –0.01–0.74	0.52 0.14–0.90	0.711	0.140	0.022

Abbreviations: ARB, angiotensin receptor blocker; BB, β-blocker; CI, confidence interval; CV, coefficient of variance; TD, thiazide diuretic.
Data are shown as the mean ± s.d. The following inclusion criteria were adopted for the *post hoc* analysis of the COPE trial: (1) subjects who did not develop any cardiovascular events within 18 months after randomization, and (2) subjects who had measured their clinic BP at least three times over at least 18 months to evaluate intra-individual visit-to-visit BP variability during the 36-month BP measurement phase. Differences in the mean, maximum, minimum, maximum–minimum, s.d. and CV of BP values between two treatment groups (ARB/BB, ARB/TD or BB/TD) were analyzed using Tukey's multiple comparison test.

maximum and minimum SBP, may be more clinically important for evaluating BP variability and predicting stroke incidence compared with DBP variability and the difference between the maximum and minimum DBP.

Several factors must be taken into account when assessing BP variability, including seasonal changes, adherence to antihypertensive treatment and BP measurement errors, as well as inappropriate dosing or titration of the antihypertensive treatment.[8] However, unlike the fixed-dose combination therapy, the treatment regimen of the COPE trial was adjusted by the BP management titration algorithm, which allowed timely adjustment of the dosage of medication and helped avoid inappropriate dosing or titration of antihypertensive medication in cases of, for example, BP variation due to seasonal changes in temperature or changes in the patients' activities.[8] This may provide better BP control, including better control of the visit-to-visit BP variability.

It remains unknown whether treatment with antihypertensive drugs should be targeted towards stabilizing BP variability, in addition to obtaining mean BP control, with the aim of optimizing cardiovascular protection. Recently, in contrast to the results of this *post hoc* analysis, visit-to-visit BP analysis of the ELSA trial demonstrated that, in mild-to-moderate hypertensive patients, carotid intima-media thickness and cardiovascular outcomes were related to the mean clinic SBP achieved by treatment but not to on-treatment visit-to-visit clinic BP variability.[21] In the COPE trial,[2–5] we mainly included relatively low-risk hypertensive patients, and the conflicting findings in relation to the association of on-treatment visit-to-visit BP variability observed in the two trials may be explained by the differences in the genetic backgrounds and/or lifestyles between Western and East Asian populations, especially in Japan, where the incidence of stroke is more common than the incidence of coronary artery disease, probably due to the high salt intake.[22–26]

Although little is currently known about the factors responsible for the long-term BP variability observed over months or years in observational studies and clinical trials of antihypertensive drugs,[8] some potential mechanisms for long-term BP variability have been postulated, including increased arterial stiffness and decreased kidney function.[27–29] We have furthermore previously reported that the hazard ratios for fatal and non-fatal stroke in older patients were significantly higher in the benidipine–β-blocker combination group compared with that in the benidipine–thiazide combination,[4] whereas in hypertensive patients with chronic kidney disease all of the benidipine-based combination therapies demonstrated comparable efficacy in terms of prevention of cardiovascular events, as well as maintenance of estimated glomerular filtration rate,[30] suggesting that increased arterial stiffness may have principally affected the results of the present study.

Study limitations

This study has some limitations that require consideration. First, we adopted the PROBE design, and the sample size of this *post hoc* analysis was relatively small in the COPE trial,[3–5,30] which might induce bias and potentially lead to chance findings. Because combination therapies are often needed for high-risk patients,[8] the optimal combination in mildly to moderately hypertensive patients should be investigated in future clinical trials.

Second, the mean of two stable measurements (difference <5 mm Hg) was regarded as the patients' clinic BP, and we obtained the clinic BP only every 6 months. Furthermore, although two different BP measurement techniques were allowed according to the guidelines for the management of hypertension,[14] the use of two different methods for clinic BP assessment might have added further confusion to the data analysis, which focused on visit-to-visit BP variability. In addition, the number of visits in the COPE trial varied among patients (a minimum of three visits was required), although the mean number of BP measurements per patient did not differ statistically between the three treatment groups during the 36-month BP measurement phase. Nonetheless, these factors may have influenced the results of the intra-individual visit-to-visit BP variability in the present study.

In conclusion, in this *post hoc* analysis of the COPE trial we first demonstrated that the combination of the CCB benidipine with thiazide may be better not only for lowering the BP level but also for reducing the intra-individual visit-to-visit BP variability compared with the benidipine–β-blocker combination. This combination may therefore provide better cardiovascular outcomes, especially in terms of a lower incidence of stroke, in hypertensive patients. However, the intra-individual visit-to-visit BP variability and cardiovascular outcomes in the benidipine–ARB combination group did not differ from those of the other two treatment regimens. Further studies to evaluate the relationships between the intra-individual BP variability and the incidence of stroke according to different drug combinations will be necessary to confirm the results of the present study.

CONFLICT OF INTEREST

All of the authors report receiving lecture fees from various pharmaceutical companies in Japan, including Kyowa Hakko Kirin, Japan.

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COMBINATION THERAPY OF HYPERTENSION TO PREVENT CARDIOVASCULAR EVENTS TRIAL GROUP

Principal study coordinator: T Ogihara.

Study adviser: T Saruta.

Steering committee: M Matsuzaki (Chairperson), T Eto, T Fujita, J Higaki, S Ito, A Kamiya, K Kikuchi, H Matsuoka, H Suzuki, C Tei.

Protocol committee: H Matsuoka (Chairperson), H Kumagai, Y Ohashi, H Rakugi, K Shimamoto, S Takishita, S Umemoto.

Endpoint classification committee: K Shimada (Chairperson), K Hayashi, K Kario, M Kawana, K Kitagawa, H Makino, M Matsumoto, J Yoshikawa.

Independent data monitoring committee: K Abe (Chairperson), H Matsuura, Y Ohashi, K Otsuka, K Tanabe.

Safety committee: N Suzuki (Chairperson), S Nogawa, K Utsunomiya, T Yoshikawa, W Yumura.

Study Statistician: Y Ohashi.

Coordinating center: S Umemoto (EBM Office, Center for Clinical Research, Yamaguchi University Hospital)

Investigators:

Hokkaido district: K Kikuchi, N Hasebe, M Bunya, W Fujii, N Funayama, M Gima, K Hashizume, Y Hirayama, H Matsuhashi, H Morimoto, T Myojo, K Ohori, H Omiya, T Ota, A Sato,

T Shiokoshi, H Tanaka, K Yamazaki, H Yoshie, K Shimamoto, M Abiru, M Adachi, Y Fujise, K Hanawa, K Ishii, Y Kadono, T Kaku, S Kaneta, M Kato, N Kato, H Kobayashi, T Komakine, T Matsumoto, T Mita, N Miura, H Mukai, K Nagao, H Nakagawa, M Nakagawa, N Nakajima, T Nishimiya, Y Nishino, A Nunokawa, J Ohata, H Ooiwa, R Sato, S Satoh, S Shibata, M Takada, Y Takagawa, Y Takagi, S Takeichi, S Tanaka, N Togashi, N Ura, C Wakabayashi, D Yoshida, H Yoshida, K Yoshida, A Kitabatake, H Tsutsui, M Akutsu, S Fujii, T Furumoto, S Kakinoki, H Kawasaki, T Kimura, M Makiguchi, H Matsuo, H Okamoto, Y Oyama, J Shimokawa, N Tsuzuki;

Tohoku district: S Ito, Y Imai, R Domon, H Ebina, S Egawa, T Haruyama, H Hashimoto, T Hayakawa, H Inomata, Y Katahira, T Katakura, R Kikuchi, H Kimura, S Kyogoku, Y Kyogoku, K Matsuo, H Nakazawa, H Odakura, F Okuguchi, E Ohtomo, H Ouchi, M Seino, M Tadokoro, Y Tanno, N Uchida, T Yamanaka, K Yunomura, K Okumura, T Hatayama, Y Kanehira, H Kaneko, M Kimura, N Maeda, A Mikuniya, H Narita, M Ono, T Osanai, M Sato;

Tokyo district: H Yoshino, S Momomura, M Ono, M Inoue, T Iwase, K Miyazaki, M Taki, T Aizawa, Y Hasunuma, H Makino, H Okabayashi, S Hosoda, T Sumiyoshi, M Abe, Y Kira, M Nagayama, K Sakai, O Yoshikawa, M Ide, N Kimura, S Matsuzaka, Y Miyajima, K Sawai, T Sumi, R Takada, M Toma, Y Yamada, K Yoda, T Yokokawa, S Yokoyama, K Kanmatsuse, T Kushiro, T Anazawa, T Ebuchi, H Fujita, N Katsumata, K Masubuchi, T Migita, T Osada, Y Otsuka, F Saito, S Shimoda, K Sugino, A Takahashi, S Tani, K Yumi, H Daida, T Arino, T Iesaki, Y Inomata, H Nakahara, H Shiraishi, H Sudo, T Degawa, T Araki, H Itaya, H Komatsu, H Kuwana, T Mikawa, H Nomoto, N Ogawa, H Sato, H Takase, H Toyoda, M Yamamoto, K Obayashi, I Akabane, H Hamamoto, R Kanbara, H Kato, H Kimura, N Mori, K Yamada, M Yamamuro, M Isobe, H Emoto, O Inaba, T Inazawa, H Inomata, K Isobe, Y Ito, M Komura, H Kosuge, Y Maejima, N Miwa, T Nishimori, K Otomo, K Sakurai, M Sawada, M Seya, M Shimizu, T Takagi, M Tamura, K Tanaka, D Tezuka, T Tokunaga, A Yagishita, A Yamashina, T Hara, S Hayashi, Y Hirayama, Y Hirooka, M Iitaka, T Ishiyama, F Kijima, H Kobayashi, Y Kobayashi, K Kondo, T Kuwabara, M Mugishima, Y Nakayama, Y Nishizato, Y Osamura, Y Sakomura, S Saneshige, N Shindo, N Takao, Y Takata, H Tomiyama, S Ishimaru, Y Obitsu, H Shigematsu, T Baba, H Fukushima, T Hirayama, K Magari, S Makimura, T Nagae, K Osada, T Osada, T Shimizu, H Suesada, K Tamura, T Yamazaki, A Hirai, T Fukasawa, H Ono, M Yamakado, T Shiba, S Otomi, A Uehata, K Takazawa, A Aizawa, T Iketani, M Kino, H Kobayashi, T Morishima, N Sakamoto, T Sakamoto, H Yamakawa, H Kasanuki, R Nagai, T Kadowaki, J Tanaka, T Yamazaki, M Takagi, S Ui, S Baba, K Fujita, T Hasegawa, K Tajima, M Tanaka, N Yamato, I Kuwajima, K Harada, H Miyata, S Mizuno, S Ueda, K Sugi, H Ando, K Mishima, M Moroi, S Nishizawa, S Suzuki, J Yamazaki, R Nakanishi, H Nakano, K Tokuyasu, T Aoyagi, M Fujioka, N Kobayakawa, K Nakajima, A Hirayama, K Tsukamoto, Y Araki, H Hara, K Hara, T Saruya;

Kanagawa district: S Umemura, M Arima, T Endo, K Furumi, Y Hatori, Y Ikeda, Y Ikeya, T Kaneda, T Kawada, T Kawano, T Kawashima, M Kihara, M Kikuta, A Kitamura, H Kobayashi, S Kobayashi, T Kuji, S Masuda, Y Minamimoto, K Minamisawa, T Mitsuhashi, N Miyazaki, Z Nagashima, T Nakatogawa, R Nakayama, N Nyui, M Ogawa, T Onishi, K Saka, T Sano, A Sato, K Shiba, F Shionoiri, H Sugiyama, H Suzuki, I Takasaki, K Tamura, Y Tokita, M Umemura, S Yamaguchi, G Yasuda;

Chiba-Saitama district: S Nakamura, K Takayanagi, T Hayashi, M Ichihara, S Kobayashi, Y Sakai, T Uchida, I Yaguchi, I Komuro, S Aoki, Y Hashimoto, C Ibuki, Y Isobe, R Kumasaka, M Matsuda, K Mizuno, D Murakami, S Nakamura, M Nakatani, T Ohba, T Ohara, T Okumura, A Saito, T Sakurai, S Sato, W Sato, K Seimiya, Y Seino, K Shimizu, M Takano, K Tokuyama, D Uchida, K Yodogawa;

Kitakanto-Koshinetsu district: S Oshima, M Kurabayashi, N Baba, Y Furushima, T Goto, T Hosoi, T Iijima, K Ito, Y Iwata, H Kubo, M Matsumoto, M Miyazaki, F Naganuma, K Nakada, M Tokushima, K Tsunoda, S Wakamatsu, Y Yagihara, Y Aizawa, M Aizawa, M Aizawa, N Hayashi, T Hori, H Kobayashi, M Kodama, K Maeda, K Miura, K Okada, Y Okura, Y Sasagawa, S Takizawa, M Tamura, T Yamamoto;

Tokai district: T Murohara, Y Awaji, H Funahashi, D Hayashi, M Iida, D Ishihara, S Ishikawa, S Kamide, M Kanashiro, N Kurebayashi, S Kyo, H Matsui, K Matsuo, M Morishima, H Noda, T Noda, N Okumura, T Ota, S Shimizu, F Somura, Y Takada, Y Takeichi, H Takezawa, T Uchikawa, D Yoshikawa, G Kimura, Y Ando, M Hoshiai, N Okuda, S Suzuki, K Takada, N Takada, K Yamada, H Hishida, T Furuta, H Hayashi, K Ito, K Kato, M Nomura, T Ota, M Ohtsuki, T Tabata, S Taga, R Tateishi, T Ito, M Fukuda, T Iwa, Y Wakida, T Yonemoto, M Watarai, M Ito, H Kawai, Y Murata, S Nomoto, K Takemoto, N Tsuboi, Y Yoshida, N Inoue, M Ishikawa, M Matsumoto, T Muramatsu, R Yoshida, M Ono, Y Hanaki, H Sano, Y Shibata, K Sakai, M Ajioka, H Asano, R Okamoto, H Osanai, Y Uemura, K Yokoi, T Tanaka, H Kamiya, K Miki, M Niwa, H Fujiwara, S Minatoguchi, T Arai, S Kato, H Kobayashi, T Minagawa, N Mori, K Nakahara, Y Shimizu, M Tadokoro, N Takahashi, T Shigemasa, I Kobayashi, T Nakano, M Ito, A Fukui, Y Higashi, T Ito, U Kano, K Makino, K Nakai, M Nakajima, T Nakajima, K Sekoguchi, T Tanaka, T Tanigawa;

Hokuriku district: N Takekoshi, H Enyama, T Hirakawa, J Ito, T Ito, H Kakuda, T Kigoshi, K Kondo, K Masuya, M Matoba, A Nakagawa, T Nakahashi, H Nakato, H Okada, M Okuro, Y Takeuchi, H Tsugawa, T Urata, M Yasuhara, M Shimizu, H Ino, T Araki, N Fujino, T Haraki, K Hayashi, S Hifumi, T Konno, M Minamoto, S Miyamoto, M Mori, C Nakanishi, Y Sakamoto, K Sakata, S Takeda, K Ueda, K Uchiyama, S Takata, S Kaneko, I Aburadani, I Inoki, K Kitano, D Kobayashi, K Kontani, M Maekawa, M Maruyama, K Matsunuma, Y Nagai, Y Nagata, M Okajima, K Otowa, Y Sekiguchi, K Shinmura, S Usui, H Yokoyama, M Yonejima;

Kinki district: K Nakao, N Hiraiwa, T Ko, I Masuda, T Nagae, K Nishino, M Sakamoto, T Kita, Y Nakagawa, T Kimura, T Doi, H Horiuchi, M Kinoshita, M Mizuno, M Ohnishi, K Shigemoto, A Wada, T Yamada, H Yoshida, M Nakagawa, H Matsubara, K Furukawa, T Hatta, A Inoue, H Katsume, A Masui, S Matsumoto, T Seki, K Takeda, Y Taniguchi, H Tsuji, Y Saito, Y Fukuoka, M Iwano, T Katsuyama, A Nakatani, Y Sakaguchi, T Konishi, T Izumi, I Toda, A Kamimoto, Y Nagai, E Matsuwaka, R Matsuwaka, K Takei, R Ueda, N Wakaki, T Iwasaka, H Hamada, S Hamada, H Koga, H Koito, K Kono, H Kurihara, J Maeda, S Morimoto, Y Takayama, T Aoyama, M Imai, T Ii, S Kashii, M Maenaka, H Ohashi, T Suyama, M Matsuda, Y Aoyagi, K Kunisada, T Mori, T Mori, J Uemura, Y Yokoi, N Morioka, T Ozaki, K Kanamasa, K Ishikawa, S Miyazaki, S Arima, T Kai, A Kurooka, I Shimada, M Takewa, M Taniguchi, R Hattori, K Haba, R Yokota, H Matsui, E Tone, H Yamahira, T Kawarabayashi, H Inaba, Y Sakaguchi, Y Yamamoto, H Ito, M Date, M Dodo, K Fujii, M Imai, K Inoue, Y Kanoh, N Komura, S Senpuku, M Takeda, H Tateyama, K Yasui, R Yoneda, H Morita, M Kawanami, A Tahara, T Sado, T Takamura, M Taniwa, Y Kitaura, M Fukuda, H Hanada, K Nakamura, K Sawada, M Yamaguchi, K Kodama, T Higo, A Hirata, M Kanzaki, S Komatsu, K Matsuo, T Murakawa, H Nakanishi,

T Nemoto, M Nishio, N Ogasawara, Y Okuyama, Y Ueda, M Imanishi, Y Kitamura, T Sakakibara, H Yoshida, H Yoshimi, T Ogihara, H Rakugi, M Akiyama, Y Ikuno, N Imai, Y Imamura, T Inoyama, K Kamide, K Katahira, S Katsuya, T Katsuya, Y Kurokawa, O Matsuki, M Matsuo, T Nakamura, E Ogura, M Ohishi, R Sasaki, K Sugimoto, J Tachi, H Tanaka, H Tanaka, T Tsunetoshi, M Yoshino, M Hori, N Awata, T Fukukawa, Y Iimori, S Iwamoto, K Sawami, M Okamura, Y Kanayama, F Nagano, H Nakayama, H Suzuki, T Amano, K Tachibana, Y Arita, M Kirino, K Sakuyama, M Shukawa, Y Nishida, T Sakamoto, S Yanagi, K Hirota, T Majima, T Ota, T Tanaka, R Nohara, T Funauchi, O Isogai, S Takashima, H Koike, M Nishimoto, Y Kawase, O Tojo, Y Chimori, H Harada, H Takeoka, S Kishi, M Yokoyama, K Hirata, J Ejiri, R Emoto, Y Furuta, K Hattori, R Kuroda, N Maehashi, H Monnaka, Y Ohashi, T Okada, H Suzuki, M Takeuchi, M Ohyanagi, M Masai, T Masuyama, M Kawabata, T Kajiya, N Daito, T Fujisawa, S Fujita, M Hasegawa, M Hirakoba, T Hirano, Y Ikeda, N Imai, K Marumoto, S Masuda, T Miki, M Mitsunaga, H Mitsuoka, Y Miyachi, N Mukohara, T Nagao, K Nakada, K Nishian, S Nishioka, T Ogura, Y Onishi, K Sakaguchi, I Sano, W Sano, M Shigenobu, A Tabuchi, J Takashima, Y Taniguchi, H Uchida, T Ueda, N Urabe;

Chugoku district: H Makino, S Harada, S Hirakawa, H Hirata, J Ishii, K Koten, Y Nagake, T Nakajima, Y Nakamura, T Terami, K Mitsudo, M Fujii, K Fujita, E Iwano, K Kadota, Y Nishihara, Y Takaya, H Yamamoto, T Yamamoto, C Shigemasa, I Hisatome, T Kato, H Miyakoda, M Sakamoto, M Shimoyama, T Shimada, K Tanabe, Y Goto, Y Hanada, K Kawakami, J Kitamura, K Kitamura, H Nakata, N Oyake, H Sugiura, H Tsukihashi, M Matsuzaki, S Umemoto, S Aoyagi, H Aoyama, T Fujino, S Fukuta, N Hiroyama, Y Ikeda, Y Inamoto, R Kametani, A Kamiya, Y Kanamaru, S Kotoku, A Matsushima, J Morita, Y Murano, M Nakatsuka, S Nishimura, Y Nisnimura, T Okamura, F Okuda, U Onaka, M Ozaki, A Shimizu, C Takata, M Tamitani, T Watada, T Watada, K Yamamoto, M Yamauchi, T Yorozu, H Yoshikane, F Yoshino;

Shikoku district: J Higaki, J Doiuchi, T Fukuoka, H Hashimoto, M Igase, H Kadota, H Kaneko, S Komatsu, Y Matsubara, K Miyoshi, K Murakami, S Murao, T Niiya, T Ochi, A Satoh, T Seki, H Takahashi, T Yamashita, T Yoshino, M Kohno, N Fujita, T Fukui, T Hamamoto, K Hasegawa, H Hitomi, K Ihara, H Kiyomoto, H Masugata, I Matsumoto, N Takahashi, K Yoshikawa, Y Doi, M Arisawa, T Egawa, M Fukuda, Y Kawada, H Kusunose, T Maeda, N Minami, M Nishinaga, T Noguchi, K Okabayashi, K Sato, T Satomi, J Takada, S Tamura, T Usui, M Yamada, M Irahara, H Azuma, M Fujimura, H Fujino, M Fujino, E Harada, S Harada, Y Hiasa, S Hosokawa, K Kawahara, K Koshiba, M Murakami, Y Nakaya, H Nii, S Nozaki, A Ota, T Ozaki, K Sone, Y Tsutsui, S Ueta;

Kyushu district: M Nobuyoshi, Y Fujishima, K Hisano, H Ikezono, R Imawatari, Y Izumi, H Kanai, T Nakamura, T Nakamura, T Noda, E Ono, S Tanaka, T Tsuiki, T Yanai, T Sasaguri, S Akimitsu, K Dohmen, K Fujisawa, K Fukuyo, S Harashima, T Hayashi, M Hirata, Y Hirata, N Ikeda, H Ikematsu, W Ikematsu, W Kajiyama, Y Kawakami, I Kawasaki, H Kondo, H Kusuhara, N Maeda, H Miyahara, A Motomura, K Nakamura, T Noguchi, T Okinaga, M Sato, I Shimada, H Shin, K Soejima, K Sugi, T Taniguchi, T Uwatoku, S Yamaga, K Yamaji, J Yanagi, H Yano, K Saku, M Enomoto, T Hiratsuka, K Imoto, R Kamei, H Kanaya, M Kohara, M Kusuda, H Nishikawa, H Sako, T Imaizumi, K Yano, K Maemura, N Ashizawa, M Hazama, Y Ishida, T Ito, M Kanda, M Kimura, T Noguchi, Y Oku, S Seto, S Suzuki, H Ogawa, K Goto, K Honjio, Y Horio, H Jinnouchi, Y Kaku, S Kawano, T Kimura, Y Kiyohara, A Maki, N Matsumoto, K Misumi, T Sakamoto, K Sasaki, S Sugiyama, E Tanaka, S Uemura, C Tei, K Arima, Y Daitoku, H Eto, T Hashino, K Ichinari, Y Ikeda, A Iriki, K Kiyonaga, K Kubota, Y Makise, S Masuzaki, M Miyata, H Mizoguchi, T Niiyama, Y Samejima, S Yonezawa.

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