

ORIGINAL ARTICLE

Effects of calcium channel blocker benidipine-based combination therapy on target blood pressure control and cardiovascular outcome: a sub-analysis of the COPE trial

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We compared three benidipine-based regimens—that is, benidipine plus angiotensin receptor blocker (ARB), β -blocker (BB) or thiazide—and found that the benidipine–BB combination was less beneficial in reducing the risk of stroke than the benidipine–thiazide combination. This sub-analysis sought to compare the effects of reaching a target blood pressure (BP) ($<140/90$ mm Hg) on the cardiovascular outcomes among the three benidipine-based treatment groups in the Combination Therapy of Hypertension to Prevent Cardiovascular Events trial. This sub-analysis included 3001 subjects to evaluate the achievement of target BP at a minimum of three points at 6-month intervals of clinical BP measurements during the study period. After randomization, the patients were categorized into two groups on the basis of achieved on-treatment target BP: a good control (GC) group achieving a BP $\geq 66.7\%$ of the target and a poor control (PC) group with a BP $<66.6\%$ of the target. For each of the two control groups, outcomes were compared among the three treatment groups. The event rates for cardiovascular composite endpoints, stroke and hard cardiovascular events were higher in the PC group than the GC group ($P=0.041$, $P=0.042$ and $P=0.038$, respectively). Within the PC group, hazard ratios for the incidence of cardiovascular events were lower in the benidipine–thiazide group than in the benidipine–BB group (composite cardiovascular events: 2.04, $P=0.033$; stroke: 4.14, $P=0.005$; and hard cardiovascular events: 3.52, $P=0.009$). Within the GC group, the incidence of cardiovascular events was not different among the three treatment regimens. The benidipine–thiazide combination may provide better cardiovascular outcomes than the benidipine–BB combination even in patients with poor BP control.

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INTRODUCTION

Previous meta-analyses have shown that anti-hypertensive agents are effective in lowering blood pressure (BP) and preventing cardiovascular events,^{1–6} but two or more agents are often required to achieve the target BP,^{7,8} and recent clinical guidelines have recommended combination therapy to control BP levels.^{9–11} Although the adverse cardiovascular consequences of hypertension largely depend on the absolute BP values,¹² current guidelines recommend $<140/90$ mm Hg as the target level of BP control based on the results of comparative studies.^{9–11}

The Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) trial was the first clinical trial to examine combination therapy with a potent and long-acting dihydropyridine calcium channel blocker (CCB), benidipine, which inhibits not only L-type and N-type calcium channels but also T-type calcium

channels,¹³ for the treatment of hypertension. In this trial, although the percentages of subjects achieving the target 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 (BB) groups, secondary analyses suggested that benidipine combined with a BB was less effective at reducing the risk of stroke compared with the benidipine–thiazide combination.^{14–18}

Many clinical trials have directly compared the effects of anti-hypertensive medications on BP reduction and cardiovascular outcomes,^{2–6} but there is little evidence concerning the effects of anti-hypertensive medications on these indices in patients with hypertension who do not achieve the target BP. Further, there are no data on the cardiovascular

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outcome of combination therapy in patients who do not achieve the target BP. In the present study, therefore, we analyzed the data on patients with hypertension who were enrolled in the COPE trial and who did not achieve the target BP following monotherapy with benidipine at a dose of 4 mg per day. We categorized these patients on the basis of their on-treatment BPs to assess the impact of not achieving the target BP (≥ 140 mm Hg) compared with achieving the target BP ($< 140/90$ mm Hg) on cardiovascular outcome among the three benidipine-based treatment groups in the COPE trial.

METHODS

Study design

The COPE trial was an investigator-initiated multi-center study with a prospective, randomized, open-label, blinded-endpoint design that compared cardiovascular effects and the achievement of a target BP ($< 140/90$ mm Hg) between three dihydropyridine-type CCB benidipine-based regimens (ARB, BB 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.^{14,15} In brief, participants aged 40–85 years with a sitting systolic BP of 140 mm Hg or more and/or a diastolic BP of 90 mm Hg or more, whether untreated or treated, who did not achieve the target BP 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 BB or a thiazide. After the randomization, all patients were followed every 6 months for at least 36 months (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 according to the guidelines for the management of hypertension.¹⁹ Mean on-treatment BP measurements were obtained at 6-month intervals from 6 months of the study treatment onwards.

The primary composite cardiovascular events consisted of the following groups: subjects with sudden death, fatal or non-fatal stroke, fatal or non-fatal myocardial infarction, hospitalization due to unstable angina, new onset of heart failure (New York Heart Association class II–IV), new onset or worsening of peripheral arterial disease, and renal events (defined as serum creatinine level doubled to over 2 mg dl⁻¹, serum creatinine ≥ 4.0 mg dl⁻¹ or renal dialysis). The secondary endpoints were defined as all-cause mortality, death from cardiovascular events, hard composite cardiovascular events (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke excluding transient ischemic attack) and new onset of diabetes.

Data analysis

A total of 3293 patients who were prescribed a combination treatment (1110, benidipine–ARB; 1089, benidipine–BB; 1094, benidipine–thiazide) were

compared using full set analysis to specifically evaluate the effects of benidipine-based combination therapy for hypertension in the COPE trial.¹⁵ BP measured on six occasions from 6 to 36 months after randomization was used to determine the achievement of target BP during the 3-year BP measurement phase from 6-month interval clinic BP measurements during the study period. After excluding 292 patients who were missing BP values for at least four out of the six measurement time points, 3001 patients (1031, benidipine–ARB; 975, benidipine–BB; 995, benidipine–thiazide) were eligible for the present study. The median percentage of target BP achieved in the subjects in this sub-analysis was 66.7%, and the previous results on the visit-to-visit BP variability in the *post-hoc* analysis of the COPE trial showed that lower visit-to-visit BP variability may be important for better outcomes.¹⁸ In consideration of all of these results on the BP control, we categorized the sub-analysis subjects into two groups based on whether they achieved on-treatment target BP of at least four points of the mean on-treatment BPs obtained at 6-month intervals from 6 months of study treatment onwards: the good control (GC) group was defined as patients who achieved a target BP $\geq 66.7\%$, and the poor control (PC) group was defined as patients who achieved target BP $< 66.6\%$ from 6 months of study treatment onwards (Figure 1). The median follow-up period was 3.67 years after randomization, and 3.1 years after the 6-month visit.

Statistical analysis

Patient characteristics were reported as the mean \pm s.d. or percentage. Continuous variables were compared with Student's *t*-tests or one-way analysis of variance, as appropriate. Categorical variables were compared with the χ^2 -test. Survival curves were generated by the Kaplan–Meier method for primary composite cardiovascular events and secondary cardiovascular events among the three treatment groups. Survival curves were compared using the

Table 1 Demographic and baseline characteristics of the cohort on the basis of achieved on-treatment blood pressure control

	Good control (n = 1733)	Poor control (n = 1268)	P-value
Sex, male	872 (50.3)	636 (50.2)	0.931
Age, years	63.2 \pm 10.4	63.4 \pm 11.0	0.574
BMI, kg m ⁻²	24.4 \pm 3.4	24.7 \pm 3.4	0.042
Systolic BP, mm Hg	151.4 \pm 10.2	157.3 \pm 12.4	<0.001
Diastolic BP, mm Hg	88.1 \pm 9.3	89.4 \pm 10.2	<0.001
Heart rate, beat per min	74.0 \pm 11.0	74.4 \pm 11.5	0.320
Previous CV disease	207 (11.9)	168 (13.2)	0.286
Diabetes	204 (11.8)	223 (17.6)	<0.001
Dyslipidemia	702 (40.5)	515 (40.6)	0.953
Current smoking	688 (39.7)	486 (38.3)	0.447
Anti-hypertensive agents	1362 (78.6)	1061 (83.7)	<0.001
Benidipine	1076 (62.1)	835 (65.9)	0.034
Other CCB	183 (10.6)	161 (12.7)	0.069
ARB	142 (8.2)	143 (11.3)	0.004
ACE inhibitor	36 (2.1)	17 (1.3)	0.130
BB	56 (3.2)	36 (2.8)	0.538
Diuretics	13 (0.8)	18 (1.4)	0.073
α -Blocker	11 (0.6)	6 (0.5)	0.560
<i>Concomitant medication</i>			
Anti-platelets	138 (8.0)	103 (8.1)	0.873
Lipid-lowering agents	378 (21.8)	261 (20.6)	0.417
Statin	303 (17.5)	203 (16.0)	0.287
Antidiabetic agents	97 (5.6)	115 (9.1)	<0.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, β -blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CV, cardiovascular. Data are shown as the number of patients (%) or mean \pm s.d. Differences in the proportions between the good and poor control groups were analyzed using the χ^2 -test or unpaired *t*-test.

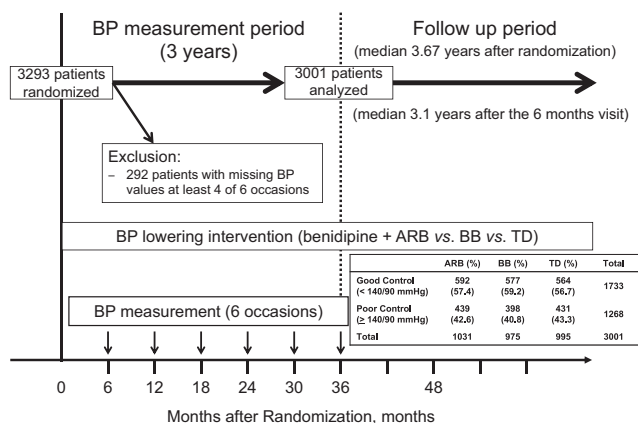


Figure 1 Flow diagram of the study participants. ARB, angiotensin receptor blocker; BB, β -blocker; TD, thiazide diuretic.

log-rank test. Hazard ratios (HRs) and confidence intervals were calculated using the Cox proportional hazards model. All data were analyzed using SAS System Release 9.1 (SAS Institute, Cary, NC, USA). All reported *P*-values are two-sided.

RESULTS

Data on the demographic and baseline characteristics showed that the body mass index, systolic and diastolic BPs, diabetes, total anti-hypertensive agents, benidipine, ARB and anti-diabetic agents were significantly higher in the PC group than the GC group (Table 1). Others characteristics were well-matched between the two groups in this sub-analysis of the COPE trial. In addition, within the GC group all of the demographic and baseline characteristics were well-matched among the three randomized groups, with the exception that the percentage of angiotensin-converting enzymes was significantly higher in the benidipine–BB group than the other two groups (Table 2).

The reduction in BP from baseline was similar among the three treatment groups in both the GC and PC groups over the course of the trial (Figure 2). At the end of the BP measurement phase, the mean average BPs in the GC and PC groups were ~128/74 mm Hg and 142/80 mm Hg, respectively. The average BP did not differ among the three treatment groups in either the GC or PC subjects. Moreover, the percentage of patients who achieved the target BP did not differ among the three treatment groups in either the GC or PC subjects, whereas the percentage of patients who achieved the target BP was higher in the GC group than in the PC group (85.9 vs. 36.1%).

Trends in the concomitant medications did not appear to differ among the three treatment groups in either the GC or PC subjects (Supplementary Table S1). However, at the 36-month follow-up, the concomitant use of lipid-lowering agents and statins was significantly higher in the PC group than the GC group (Supplementary Table S2).

Hazard ratios

The event rates for the primary composite cardiovascular events, hard composite cardiovascular events and stroke were significantly higher in the PC group than in the GC group (Table 3): the HRs of primary composite cardiovascular events, hard composite cardiovascular events, and stroke were significantly higher in the benidipine–BB group than in the benidipine–thiazide group of the PC group, whereas they did not differ among the three treatment groups of the GC group. We further calculated the HRs by the multi-adjusted and adjusted with the systolic BP with time-dependent covariates in this sub-analysis for the primary composite cardiovascular events, hard composite cardiovascular events and stroke (Supplementary Table S3), demonstrating that the results of this sub-analysis of the COPE trial confirmed that the influence of the BP difference among the three treatment groups in the PC group on outcomes was negligible. In contrast, compared with the benidipine–ARB group, the HR of the incidence of new-onset diabetes was significantly higher in the benidipine–BB group than in the other two treatment groups in the GC group, whereas it did not differ among the three treatment groups of the PC group (Figure 3). In contrast, the HRs of cardiac events and all-cause mortality were not

Table 2 Demographic and baseline characteristics of the cohort on the basis of achieved on-treatment target blood pressure control

	Good control				Poor control			
	Benidipine plus ARB (n = 592)	Benidipine plus BB (n = 577)	Benidipine plus TD (n = 564)	P- value	Benidipine plus ARB (n = 439)	Benidipine plus BB (n = 398)	Benidipine plus TD (n = 431)	P- value
Sex, male	297 (50.2)	287 (49.7)	288 (51.1)	0.901	226 (51.5)	200 (50.3)	210 (48.7)	0.718
Age, years	62.5 ± 10.3	63.4 ± 10.5	63.8 ± 10.3	0.093	63.8 ± 11.0	63.3 ± 11.0	63.1 ± 11.1	0.675
BMI, kg m ⁻²	24.6 ± 3.4	24.4 ± 3.4	24.4 ± 3.4	0.661	24.8 ± 3.4	24.9 ± 3.4	24.4 ± 3.3	0.099
Systolic BP, mm Hg	151.0 ± 10.6	151.4 ± 9.6	151.7 ± 10.2	0.525	157.6 ± 12.2	156.8 ± 11.7	157.4 ± 13.2	0.656
Diastolic BP, mm Hg	88.5 ± 9.2	88.0 ± 9.4	87.9 ± 9.3	0.531	89.7 ± 10.4	89.2 ± 9.9	89.3 ± 10.3	0.736
Heart rate, beat per min	73.9 ± 11.1	74.7 ± 10.9	73.3 ± 11.0	0.140	74.1 ± 11.2	73.8 ± 11.1	75.4 ± 12.1	0.146
Previous CV disease	66 (11.1)	63 (10.9)	78 (13.8)	0.242	67 (15.3)	49 (12.3)	52 (12.1)	0.305
Diabetes	67 (11.3)	65 (11.3)	72 (12.8)	0.671	78 (17.8)	74 (18.6)	71 (16.5)	0.720
Dyslipidemia	238 (40.2)	235 (40.7)	229 (40.6)	0.982	164 (37.4)	159 (39.9)	192 (44.5)	0.092
Current smoking	234 (39.5)	220 (38.1)	234 (41.5)	0.507	168 (38.3)	161 (40.5)	157 (36.4)	0.492
Anti-hypertensive agents	462 (78.0)	456 (79.0)	444 (78.7)	0.915	367 (83.6)	331 (83.2)	363 (84.2)	0.918
Benidipine	364 (61.5)	363 (62.9)	349 (61.9)	0.875	287 (65.4)	262 (65.8)	286 (66.4)	0.954
Other CCB	65 (11.0)	60 (10.4)	58 (10.3)	0.918	56 (12.8)	50 (12.6)	55 (12.8)	0.995
ARB	47 (7.9)	48 (8.3)	47 (8.3)	0.962	47 (10.7)	47 (11.8)	49 (11.4)	0.878
ACE inhibitor	15 (2.5)	11 (1.9)	10 (1.8)	0.623	2 (0.5)	12 (3.0)	3 (0.7)	0.002
BB	13 (2.2)	20 (3.5)	23 (4.1)	0.180	11 (2.5)	15 (3.8)	10 (2.3)	0.398
Diuretics	3 (0.5)	4 (0.7)	6 (1.1)	0.538	7 (1.6)	4 (1.0)	7 (1.6)	0.700
α-Blocker	2 (0.3)	7 (1.2)	2 (0.4)	0.101	3 (0.7)	3 (0.8)	0 (0.0)	0.209
<i>Concomitant medication</i>								
Anti-platelets	43 (7.3)	46 (8.0)	49 (8.7)	0.670	47 (10.7)	27 (6.8)	29 (6.7)	0.050
Lipid-lowering agents	132 (22.3)	125 (21.7)	121 (21.5)	0.936	87 (19.8)	82 (20.6)	92 (21.3)	0.856
Statin	106 (17.9)	103 (17.9)	94 (16.7)	0.824	69 (15.7)	68 (17.1)	66 (15.3)	0.769
Anti-diabetic agents	31 (5.2)	28 (4.9)	38 (6.7)	0.343	40 (9.1)	41 (10.3)	34 (7.9)	0.481

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, β-blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CV, cardiovascular.

Data are shown as the number of patients (%) or mean ± s.d. Differences in the proportions between the good and poor control groups were analyzed using the χ^2 -test or one-way analysis of variance.

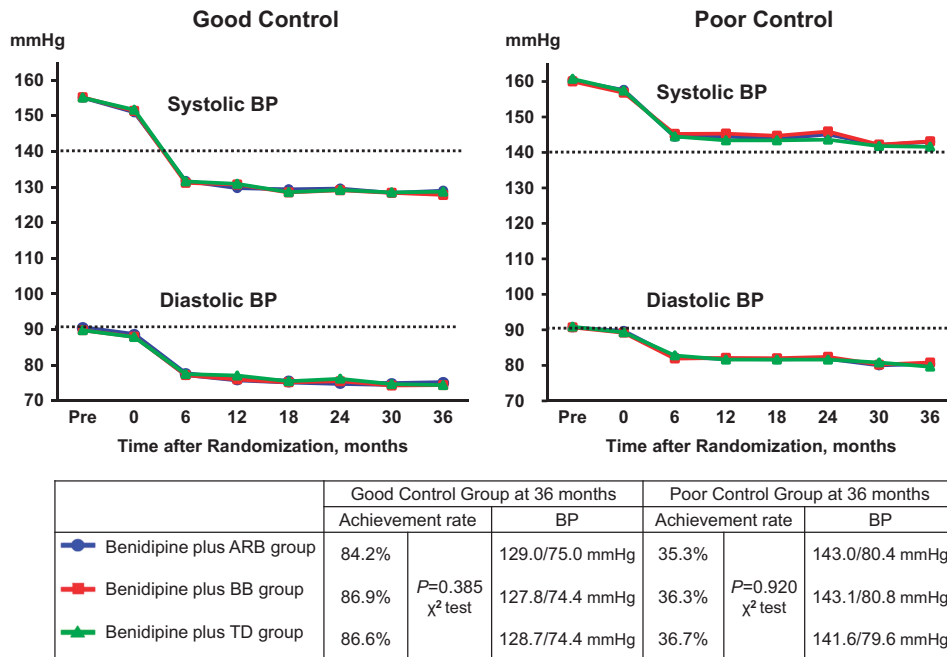


Figure 2 Effects of treatment on mean systolic and diastolic BP and achievements of target BP. ARB, angiotensin receptor blocker; BB, β -blocker; BP, blood pressure; TD, thiazide diuretic. Data of the proportions of target blood pressure are shown as percentage of patients. Achievement rate is the proportion of patients achieving target BP (systolic BP < 140 mm Hg and diastolic BP < 90 mm Hg).

Table 3 Incidence of primary and secondary endpoints

	Good control (n = 1733)	Poor control (n = 1268)	P-value (log-rank)
<i>Primary endpoints</i>			
Composite cardiovascular events	53 (8.2)	56 (12.1)	0.041
<i>Secondary endpoints</i>			
Hard composite cardiovascular events	27 (4.1)	33 (7.1)	0.038
Fatal and non-fatal stroke including TIA	21 (3.2)	27 (5.8)	0.042
Cardiac events	24 (3.7)	25 (5.3)	0.196
All-cause mortality	33 (5.0)	28 (5.9)	0.474
New-onset diabetes	56 (8.7)	34 (7.3)	0.397

Abbreviation: TIA, transient ischemic attack.

Hard composite cardiovascular events were consist of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Differences in the primary and secondary events between the good control group and the poor control group were analyzed using Tukey's multiple comparison test. Data are shown as incidence number (per 1000 patients years).

different among the three treatment groups in both the GC and PC groups.

Primary and secondary outcomes

The survival curves for time to first composite cardiovascular endpoints, hard composite endpoints and stroke in both the PC and GC groups (Figure 4) showed that compared with the benidipine–thiazide group of the PC group, primary composite cardiovascular endpoints (Figure 4a), hard composite cardiovascular events (Figure 4b) and stroke (Figure 4c) were significantly higher only in the benidipine–BB group, whereas the difference in these endpoints among the three treatment groups did not differ in the GC group. The incidence of the primary composite cardiovascular endpoints, hard composite cardiovascular events and stroke in the benidipine–ARB group was higher than in the benidipine–thiazide group and lower than the benidipine–BB group, but the incidence of these endpoints in the benidipine–ARB regimen did not differ from the benidipine–thiazide or the benidipine–BB group in both the PC and GC groups (Figure 4).

Adverse events

The percentage of total adverse events was similar in both the PC and GC groups: 613 (48.3%) and 613 (48.3%) patients reported adverse events, respectively (Supplementary Table S4). In addition, the percentage of total adverse events was also similar among the three treatment groups in both the PC and GC groups (Supplementary Table S4). In the PC group, the following adverse events were more frequent than in the GC group: increased glycosylated hemoglobin (1.6 and 0.6%; $P < 0.012$); proteinuria (1.5 and 0.7%; $P = 0.031$); cardiac failure (0.9 and 0.2%; $P < 0.006$); and thrombotic stroke (0.7 and 0.1%; $P = 0.008$), as shown in Supplementary Table S4.

DISCUSSION

The most important and surprising findings in this sub-analysis from the COPE trial were that the benidipine–thiazide combination may provide better cardiovascular outcome than the benidipine–BB combination even in patients with poor BP control, whereas no significant differences on cardiovascular outcome were observed

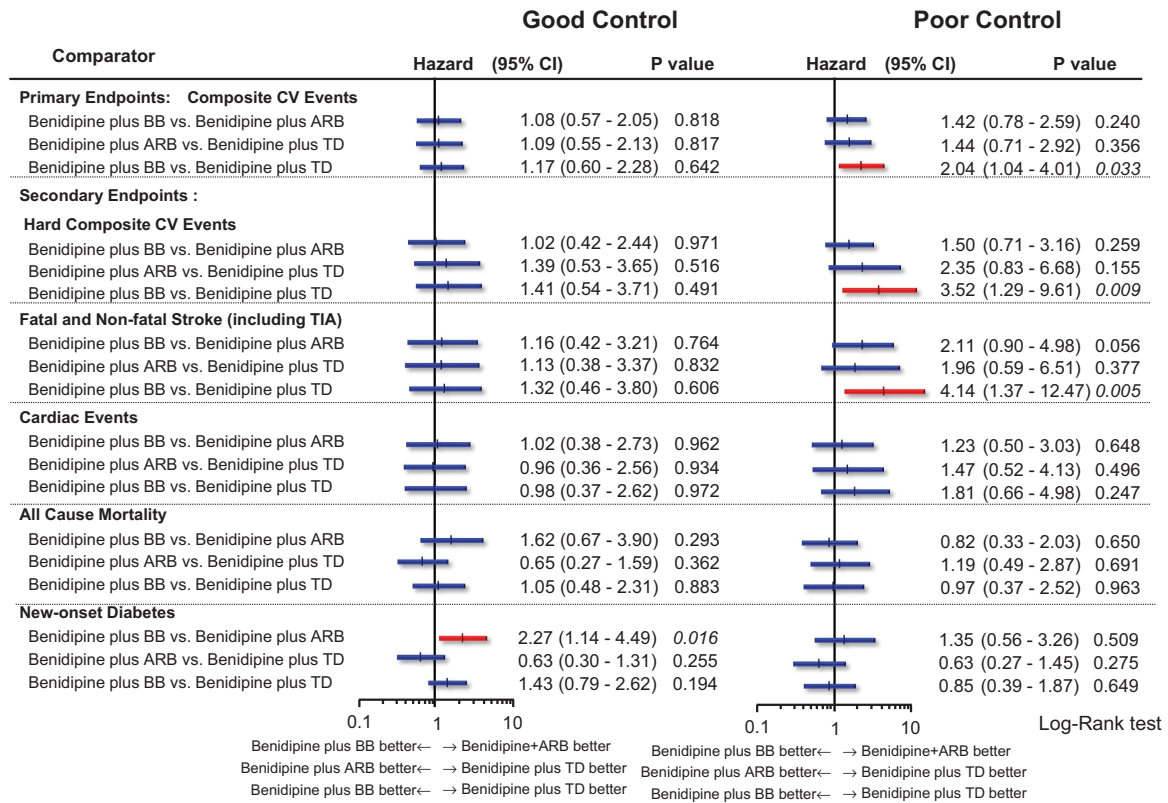


Figure 3 Hazard ratios for primary and secondary endpoints. A primary composite cardiovascular events consisted of the following groups: sudden death; fatal or non-fatal stroke; fatal or non-fatal myocardial infarction; hospitalization due to unstable angina; new onset of heart failure (New York Heart Association class II–IV); new onset or worsening of peripheral arterial disease; and renal events (defined as serum creatinine level doubled to over 2 mg dl⁻¹, serum creatinine ≥ 4.0 mg dl⁻¹ or renal dialysis). Hard composite cardiovascular events consist of cardiovascular death, fatal or non-fatal myocardial infarction and stroke excluding TIA. ARB, angiotensin receptor blocker; BB, β-blocker; CI, confidence interval; CV, cardiovascular; TD, thiazide diuretic; TIA, transient ischemic attack.

among the three benidipine-based combinations in the patients with good BP control.

Current guidelines for the management of hypertension^{9,11,20} recommend a BP < 140/90 mm Hg as a target BP to reduce the incidence of cardiovascular disease. In this sub-analysis, we confirm that the achievement of this target BP is important and that the three allocated classes of anti-hypertensive agents used in the COPE trial are suitable for the CCB, benidipine-based combination to reduce the incidence of cardiovascular disease when sufficiently achieving the target BP. In contrast, when the target BP is insufficiently achieved throughout the BP measurement phase by the benidipine-based combinations, the benidipine–thiazide regimen may be better to prevent the incidence of cardiovascular outcome than the benidipine–BB regimen even if the mean BPs are higher than the target BP. We recently reported that the benidipine–thiazide combination may reduce intra-individual visit-to-visit BP variability more than the benidipine–BB combination,¹⁸ suggesting that visit-to-visit BP variability is greater when mean BP is higher.²¹ These findings indicate that even when target BP is insufficiently achieved, the reduction of intra-individual visit-to-visit BP variability may be important to reduce cardiovascular events in patients with hypertension.

In this sub-analysis of the COPE trial, the mean average BPs at the end of the BP measurement phase in the GC and PC groups were ~ 128/74 mm Hg and 142/80 mm Hg, respectively. In addition, the cardiovascular event rates for the benidipine–thiazide combination in the PC group were similar to the cardiovascular event rates for this

combination in the GC group (Figure 4). Recently, the SPRINT Research Group²² reported that among patients at high risk for cardiovascular events but without diabetes, targeting a systolic BP < 120 mm Hg, compared with < 140 mm Hg, resulted in lower rates of fatal and non-fatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group. In their study, the drugs were mainly dihydropyridine-type CCBs, angiotensin-converting enzyme inhibitors or ARBs, and diuretics and the mean systolic BP at 1 year was 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group. Although the COPE trial¹⁵ mainly included lower-risk patients with fewer cardiovascular complications compared with those in the SPRINT research,²² the SPRINT sub-analysis also showed lower rates of fatal and non-fatal major cardiovascular events in the GC group, indicating that the results of our sub-analysis may support the results of the SPRINT research.²² Moreover, the benidipine–thiazide combination may result in better cardiovascular outcomes in hypertensive patients compared with the benidipine–BB combination, when the target BP was insufficiently achieved.

Study limitations

We adopted the prospective, randomized, open-label, blinded-endpoint design and the sample size and cardiovascular events of this sub-analysis of the COPE trial were relatively small,^{15–17,23} which could have induced a bias and led to chance findings. Because

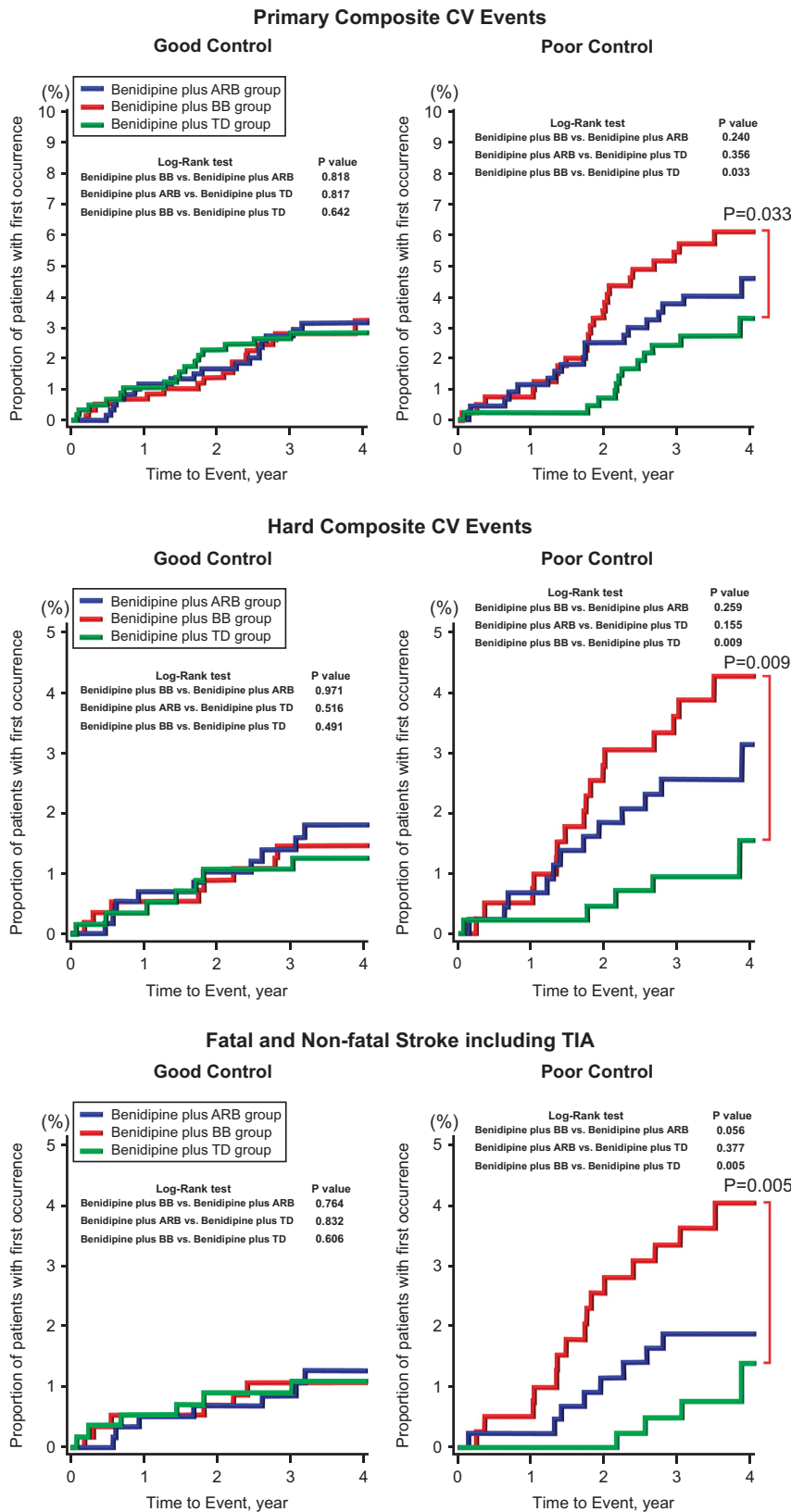


Figure 4 Kaplan-Meier curves for time to first primary and secondary endpoint. Primary composite cardiovascular events: sudden death, fatal or non-fatal stroke, fatal or non-fatal myocardial infarction, hospitalization due to unstable angina, new onset of heart failure (New York Heart Association class II–IV), new onset or worsening of peripheral arterial disease, and renal events (defined as serum creatinine level doubled to over 2 mg dl⁻¹, serum creatinine ≥4.0 mg dl⁻¹, or renal dialysis). Hard composite cardiovascular events; cardiovascular death, non-fatal myocardial infarction and non-fatal stroke excluding transient ischemic attack. ARB, angiotensin receptor blocker; BB, β-blocker; CV, cardiovascular; TD, thiazide diuretic; TIA, transient ischemic attack.

combination therapies are often needed for high-risk patients,²¹ the optimal combination in mildly to moderately hypertensive patients should be investigated in future clinical trials. In addition, this sub-analysis of a randomized trial was not specifically designed to test various BP targets. Moreover, the results are applicable only to hypertensive patients 40–85 years of age with a BP of $\geq 140/90$ after benidipine-based monotherapy at entry. 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 significantly between the 3 treatment groups during the 36-month BP measurement phase.

CONCLUSIONS

In this sub-analysis of the COPE trial, the benidipine–thiazide combination provided better cardiovascular outcome than the benidipine–BB combination even in subjects with poor BP control. Indeed, we demonstrated that this combination may be better not only for lowering the BP level but also for reducing stroke and other cardiovascular events compared with the benidipine–BB combination. This may be true even in patients who have insufficiently achieved the target BP ($\geq 140/90$ mm Hg). Hence, this combination may provide better cardiovascular outcomes, especially in terms of stroke incidence, in hypertensive patients. However, the reduction of BP and the achievement of target BP and cardiovascular outcomes in the benidipine–ARB combination group did not differ from those of the other two treatment regimens. Although recent guidelines recommend the combination of CCBs and thiazide diuretics,^{9,11,20} this combination is not widely used in current clinical practice. In fact, only four studies on this combination have been reported,^{15,24–26} and a meta-analysis of the results showed a significant risk reduction for myocardial infarction and stroke compared with other combinations, whereas the effectiveness of this therapy was similar to that of other combinations in terms of reducing the risk of all-cause and cardiovascular mortality.²⁷ Further studies to evaluate the CCB–thiazide combination and the incidence of stroke in comparison with other drug combinations will be needed to confirm the results of the present study.

CONFLICT OF INTEREST

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