

Preferable effects of olmesartan/calcium channel blocker to olmesartan/diuretic on blood pressure variability in very elderly hypertension: COLM study subanalysis

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Objective: The aims of this subanalysis of the COLM trial [NCT00454662] were to compare visit-to-visit variability (VVV) of blood pressure (BP) between age groups and between two treatment combinations, that is, the angiotensin II receptor blocker, olmesartan combined with a calcium channel blocker (CCB), or a diuretic and to investigate the effect of VVV of BP on cardiovascular events in elderly hypertensive patients.

Methods: Hypertensive patients ages 65–84 years with a history of and/or risk factors for cardiovascular disease were randomized to receive treatment with olmesartan along with either a CCB or a diuretic for at least 3 years. This subanalysis comprised 4876 patients who had their office BP measured at least three occasions (median nine occasions) during the follow-up period. VVV of BP was defined by several metrics including the within-individual standard deviation of every visit during the follow-up period.

Results: VVV of SBP was larger in the very elderly group (75–84 years) than in the elderly group (65–74 years). VVV of SBP was smaller in the olmesartan along with CCB group than in the olmesartan along with diuretic group, especially in very elderly patients and also isolated systolic hypertensive patients. The incidence rate of primary endpoint increased along with an increment in the SD of SBP in all of the age and treatment groups.

Conclusion: VVV of SBP may mediate the preferable effect of combination of angiotensin II receptor blocker along with CCB on cardiovascular events in the very elderly and also isolated systolic hypertensive patients.

Keywords: angiotensin II receptor blocker, calcium channel blocker, combination therapy, diuretics, elderly hypertension, isolated systolic hypertension, visit-to-visit variability of blood pressure

Abbreviations: ARB, angiotensin II receptor blocker; ARV, average real variability; BP, blood pressure; CCB, calcium channel blocker; CI, confidence interval; COLM trial, Combination of OLMesartan and a calcium channel blocker or a diuretic in Japanese elderly hypertensive

patients trial; ISH, isolated systolic hypertension; SD, standard deviation; SDIM, standard deviation independent of the mean; VVV, visit-to-visit variability

INTRODUCTION

Antihypertensive treatment for elderly hypertensive patients has been demonstrated to significantly reduce both the incidence of cardiovascular events and mortality [1]. However, many hypertensive patients require treatment with two or more antihypertensive agents to achieve the target blood pressure (BP) recommended by guidelines for the management of hypertension [2–4]. Although several trials have demonstrated the effectiveness of some combination therapies for elderly hypertensive individuals [5–7], it remains unclear what kinds of combinations are more suitable for elderly hypertensive patients.

The Combination of OLMesartan and a calcium channel blocker (CCB) or a diuretic in Japanese elderly hypertensive patients (COLM) trial was a prospective, randomized, open-label, blinded-endpoint study that investigated the preferable combination therapy for high-risk elderly hypertensive patients by comparing treatment with an angiotensin II receptor blocker (ARB) along with a CCB or an ARB along

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with a diuretic. This study showed that there was no significant difference of the primary composite endpoint (cardiovascular morbidity and mortality) between the two treatment groups [8,9].

A prespecified subgroup analysis of the COLM trial [10] demonstrated that olmesartan along with CCB therapy may be preferable to olmesartan along with diuretic therapy for preventing cardiovascular events in very elderly patients (75–84 years), although there was no significant difference of BP between the two groups at the end of treatment. In contrast, there was no significant difference of the primary composite endpoint between elderly patients (65–74 years) from these two treatment groups. However, the mechanisms underlying the superiority of olmesartan along with CCB therapy for preventing cardiovascular events in very elderly hypertensive patients are unclear.

The visit-to-visit variability (VTV) of BP was recently reported to show a significant correlation with atherosclerosis or the cardiovascular prognosis independently of BP or other risk factors [11–14]. Therefore, we hypothesized that VTV of BP could be a possible mechanism that explains the superiority of ARB along with CCB therapy over ARB along with diuretic therapy in very elderly hypertensive patients from the COLM trial [10]. To test this hypothesis, we compared VTV of SBP between elderly patients and very elderly patients, as well as between olmesartan along with CCB group and the olmesartan along with diuretic group, using data from the COLM trial. We also investigated whether these effects on VTV of BP were associated with preferable effect of the combination of olmesartan along with CCB vs. olmesartan along with diuretic on cardiovascular events in very elderly patients.

METHODS

Study design

The rationale and design, management, and principal results of the COLM trial have been published previously [8,9]. An outline of the COLM trial is described below. Hypertensive patients ages 65–84 years with a history of cardiovascular disease and/or cardiovascular risk factors and an SBP was equal to or higher than 140 mmHg and/or DBP was equal to or higher than 90 mmHg on antihypertensive treatment (or SBP was equal to or higher than 160 mmHg and/or DBP was equal to or higher than 100 mmHg without antihypertensive treatment) were randomized to receive treatment with olmesartan along with either a CCB (amlodipine or azelnidipine) or a low-dose diuretic (trichlormethiazide, indapamide, or another thiazide) for at least 3 years. The target BP was less than 140/90 mmHg. The median follow-up period was 3.3 years.

The COLM trial was conducted in accordance with the Declaration of Helsinki, and its protocol was approved by the institutional review board of each participating center. The trial was conducted from April 2007 to September 2011 at 707 primary care and cardiology centers in Japan.

The present subanalysis comprised 4876 patients (94.8% of original trial) in whom the office BP was measured at least three occasions during the follow-up period (mean: 8.2 ± 1.71 occasions, median: nine occasions). The endpoints evaluated were consistent with those of the original

trial. The primary endpoint was a composite of cardiovascular morbidity and mortality (sudden death, fatal or non-fatal stroke, fatal or nonfatal myocardial infarction, coronary revascularization, hospitalization for angina pectoris or heart failure, and renal events). All cardiovascular events reported by the participating physicians were adjudicated by the endpoint committee, which was blinded to the study group. VTV of BP was defined by using the standard deviation (SD) of the BP at every visit during follow-up. We calculated additionally three other metrics as VTV of BP; standard deviation independent of the mean (SDIM), peak value, and average real variability (ARV) [15].

Statistical analysis

All statistical analyses were conducted using SAS 9.1 software (SAS Institute Inc., Cary, North Carolina, USA). Results are presented as the mean \pm SD or as percentages. Differences of baseline characteristics or VTV of BP between the groups were analyzed by Fisher's exact test or the unpaired *t* test, as appropriate. A stratified proportional hazards model was used to estimate the hazard ratio and its 95% confidence interval (CI) for quartiles of VTV of SBP with sex and a history of cardiovascular disease as the stratification variables and mean SBP as the covariate. The log-rank trend test was used to compare the incidence rates of the primary endpoint among quartiles based on VTV of SBP. The Cochran–Mantel–Haenszel statistics was performed to assess the distribution of quartiles for VTV of SBP in each group. To examine the three-factor interactive effects of predictors on cardiovascular events, stratified proportional hazards models, which included mean SBP, VTV, age-class, treatment arm, VTV*age-class, VTV*treatment-arm, and VTV*age-class*treatment-arm as covariates were used, stratifying with sex, and a history of cardiovascular disease.

RESULTS

We compared baseline characteristics between the elderly group (patients of 65–74 years, $n=2778$, mean age of 69.6 ± 2.9 years) and the very elderly group (patients of 75–84 years, $n=2098$, mean age of 78.8 ± 2.8 years), as well as between each age group of the two treatment groups (Table 1). There was no significant difference of SBP between the two age groups, but the very elderly group had a significantly lower DBP and higher prevalence of systolic hypertension than the elderly group. In addition, the very elderly group was significantly more likely to have a history of cardiovascular events and also had a higher prevalence of left ventricular hypertrophy than the elderly group. In contrast, comparison between two treatment groups in each age group showed no significant differences of baseline characteristics, the severity of hypertension, a history of cardiovascular disease, and cardiovascular risk factors, except for the prevalence of dyslipidemia in the very elderly group.

Compared with the elderly group, the SD of SBP was significantly larger in the very elderly group (Table 2). The very elderly group also had a significantly larger SD of DBP (7.08 ± 3.24 vs. 6.73 ± 3.03 , $P < 0.001$). In the olmesartan along with CCB group, very elderly group had a significantly larger SD of SBP (Table 2) and SD of DBP (7.04 ± 3.29

TABLE 1. The comparison of baseline characteristic and blood pressure during the follow-up period

	Elderly patients (n = 2778)			Very elderly patients (n = 2098)			P between age groups
	Olmesartan along with CCB (N = 1399)	Olmesartan along with diuretic (N = 1379)	P	Olmesartan along with CCB (N = 1057)	Olmesartan along with diuretic (N = 1041)	P	
Sex, male	55.2%	56.1%	0.62	45.8%	45.5%	0.93	<0.001
Age (years)	69.7 ± 2.9	69.5 ± 2.9	0.10	78.8 ± 2.8	78.9 ± 2.8	0.71	<0.001
SBP (mmHg)	157.8 ± 12.6	157.9 ± 12.6	0.88	157.5 ± 12.3	157.6 ± 12.1	0.93	0.45
DBP (mmHg)	88.6 ± 10.5	88.8 ± 10.4	0.56	84.8 ± 10.6	84.4 ± 10.7	0.29	<0.001
Heart rate (bpm)	72.4 ± 9.5	72.4 ± 9.0	0.90	73.8 ± 10.3	73.2 ± 9.6	0.15	<0.001
BMI (kg/m ²)	24.7 ± 3.5	24.6 ± 3.4	0.61	24.0 ± 3.4	23.8 ± 3.4	0.20	<0.001
Grade of hypertension							
Grade 1	54.2%	55.3%	0.68	58.8%	58.7%	0.51	0.047
Grade 2	40.2%	38.4%		34.9%	36.3%		
Grade 3	5.2%	6.0%		5.8%	4.7%		
Isolated systolic hypertension	52.8%	50.6%	0.25	65.0%	67.5%	0.23	<0.001
Previous history of cardiovascular events	21.4%	20.8%	0.74	27.2%	28.3%	0.56	<0.001
Stroke	12.9%	13.9%	0.50	16.5%	16.9%	0.81	0.002
Ischemic heart disease	9.6%	8.5%	0.32	13.3%	13.5%	0.85	<0.001
Cardiovascular risk factors							
Left ventricular hypertrophy	8.4%	8.9%	0.64	11.7%	10.6%	0.41	0.004
Diabetes mellitus	27.4%	26.7%	0.70	25.8%	25.9%	0.96	0.38
Dyslipidemia	48.6%	45.4%	0.09	42.2%	47.3%	0.02	0.11
Smoker	28.8%	30.4%	0.34	20.1%	19.4%	0.74	<0.001
Drinking	50.4%	50.6%	0.91	32.9%	32.1%	0.74	<0.001
Number of visits, median	9.0	9.0	–	9.0	9.0	–	–
Number of visits, mean ± SD	8.29 ± 1.63	8.25 ± 1.69	0.49	8.13 ± 1.78	8.07 ± 1.79	0.42	<0.001
SBP during the follow-up period (mmHg)	136.3 ± 10.0	135.4 ± 10.2	0.028	135.7 ± 9.6	136.7 ± 10.9	0.029	0.19
DBP during the follow-up period (mmHg)	76.5 ± 7.3	76.5 ± 7.3	0.85	73.3 ± 7.4	74.2 ± 7.4	0.004	<0.001

The comparison of baseline characteristics by treatment group in each age group. Elderly, 65–74 years; very elderly, 75–84 years. Stroke includes cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage. Ischemic heart disease includes myocardial infarction, angina pectoris, and history of percutaneous coronary intervention/coronary artery bypass grafting. CCB, calcium channel blocker; SD, standard deviation.

vs. 6.63 ± 3.02 , $P=0.001$) than elderly group. In the olmesartan along with diuretic group, very elderly group also had a significantly larger SD of SBP (Table 2) and SD of DBP (7.11 ± 3.18 vs. 6.84 ± 3.04 , $P=0.03$) than elderly group.

We classified the participants into four groups according to the SD of SBP (the SD of SBP in the first to fourth quartiles was ≤ 6.155 , $6.156-9.433$, $9.434-13.309$, and ≥ 13.310 mmHg, respectively) and compared the incidence rate of the primary endpoint among them. As a result, the incidence rate of the primary endpoint showed an increase that was associated

with elevation of the SD of SBP in both elderly group (P for trend <0.001) and very elderly group (P for trend <0.001) (Fig. 1). To compare the distribution of age groups across the quartiles for the SD of SBP, we used the Cochran–Mantel–Haenszel statistics, which revealed that very elderly group accounted for a significantly larger distribution of the higher quartiles than elderly group ($P<0.001$) (Supplementary Figure 1 <http://links.lww.com/HJH/A499>).

Overall, the olmesartan along with CCB group showed a significantly smaller SD of SBP compared with the

TABLE 2. Effects of age and treatment on the standard deviation of SBP

	Olmesartan along with CCB	Olmesartan along with diuretic	All	P between treatment groups
All patients				
Elderly (n = 2778)	9.67 ± 5.16	9.98 ± 5.37	9.83 ± 5.27	0.121
Very elderly (n = 2098)	10.48 ± 5.48	11.08 ± 6.04	10.78 ± 5.77	0.018
All (n = 4876)	10.02 ± 5.31	10.46 ± 5.69	10.24 ± 5.51	0.006
P value between age groups	<0.001	<0.001	<0.001	
Isolated systolic hypertensive patients				
Elderly (n = 1437)	10.12 ± 5.27	10.68 ± 5.37	10.39 ± 5.33	0.048
Very elderly (n = 1390)	11.06 ± 5.23	11.88 ± 6.11	11.48 ± 5.70	0.007
All (n = 2827)	10.57 ± 5.27	11.28 ± 5.78	10.93 ± 5.54	<0.001
P value between age groups	<0.001	<0.001	<0.001	
Nonisolated systolic hypertensive patients				
Elderly (n = 1341)	9.17 ± 4.98	9.27 ± 5.28	9.22 ± 5.13	0.72
Very elderly (n = 708)	9.41 ± 5.77	9.40 ± 5.55	9.41 ± 5.66	0.98
All (n = 2049)	9.26 ± 5.28	9.31 ± 5.37	9.28 ± 5.32	0.81
P value between age groups	0.47	0.71	0.44	

Comparison the visit-to-visit variability of SBP (SD of SBP) between the elderly and very elderly groups and between the olmesartan along with CCB and olmesartan along with diuretic groups. Differences in the SD of SBP between groups were analyzed using unpaired *t* test. Elderly, 65–74 years; very elderly, 75–84 years. CCB, calcium channel blocker; SD, standard deviation.

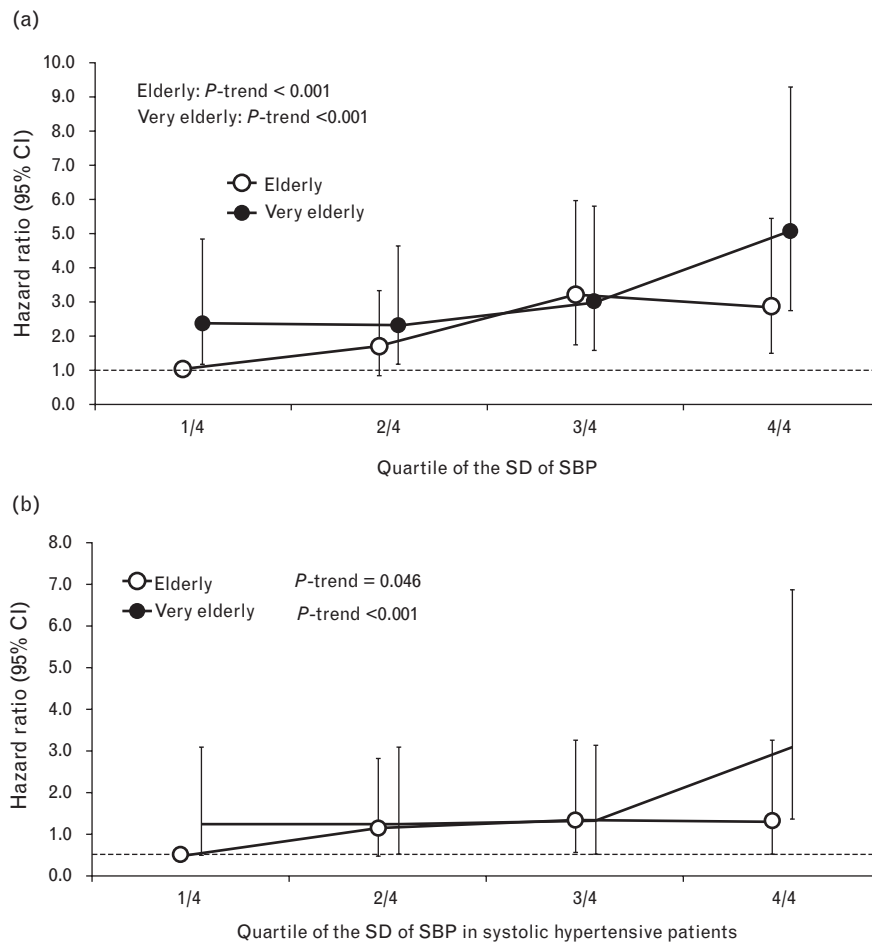


FIGURE 1 Association between the SD of SBP and the hazard ratio for the primary endpoint in the elderly and very elderly groups. The hazard ratio was adjusted for sex and a history of cardiovascular diseases as stratification variables and for mean SBP as the covariate. (a) All patients, and (b) patients with ISH. Elderly, 65–74 years; very elderly, 75–84 years. CI, confidence interval; ISH, isolated systolic hypertension; SD, standard deviation.

olmesartan along with diuretic group ($P=0.006$) (Table 2). The SD of DBP did not show significant difference between two the treatment groups (6.81 ± 3.14 in the olmesartan along with CCB vs. 6.95 ± 3.10 in the olmesartan along with diuretic, $P=0.10$). When analyzed by age group, olmesartan along with CCB group was associated with a significantly lower SD of SBP than olmesartan along with diuretic group ($P=0.018$) in very elderly group, but there was no such significant difference in elderly group ($P=0.12$) (Table 2). Differences of the SD of DBP between the olmesartan along with CCB and the olmesartan along with diuretic groups were not significant both in elderly (6.63 ± 3.02 vs. 6.84 ± 3.04 , $P=0.07$) and very elderly (7.04 ± 3.29 vs. 7.11 ± 3.18 , $P=0.64$) groups.

For further exploratory analyses whether high VVV mediated the effect of the two drug combinations on cardiovascular events, we compared the incidence of the primary endpoint among the quartiles of the SD of SBP. This analysis showed that the incidence rate of the primary endpoint increased along with an increment in the SD of SBP for elderly group (Fig. 2a) and very elderly group (Fig. 2b) from both treatment groups. The Cochran–Mantel–Haenszel statistics revealed that there were significantly fewer very elderly patients from the olmesartan along with CCB group than the olmesartan along with diuretic group in

the higher quartiles for the SD of SBP ($P=0.017$) (Supplementary Figure 2b <http://links.lww.com/HJH/A499>), whereas there was no significant difference for elderly group ($P=0.11$) (Supplementary Figure 2a <http://links.lww.com/HJH/A499>). In addition, we examined the three-factor interactive effects of predictors on cardiovascular events using stratified proportional hazards models. Three-factor interaction, SD of SBP*age-class*treatment-arm, was statistically significant for composite of hard endpoints ($P=0.045$) and stroke ($P=0.042$). These results indicate that the SD of SBP mediates the effect of the drug combinations and the age groups on cardiovascular events.

Other metrics of VVV of SBP such as SDIM, peak size, and ARV of SBP showed almost same results with SD of SBP; larger in the very elderly group than in the elderly group, smaller in the olmesartan along with CCB group than in the olmesartan along with diuretic group among very elderly patients, and association of larger VVV of SBP with higher incidence of cardiovascular events with regardless of age or treatment except peak size in both age groups and ARV in very elderly treated with olmesartan along with diuretic (Supplemental Table 1 <http://links.lww.com/HJH/A499> and Supplemental Figure 1 <http://links.lww.com/HJH/A499>). A model in which these VVV, mean SBP, age-class, and treatment arm were included showed that

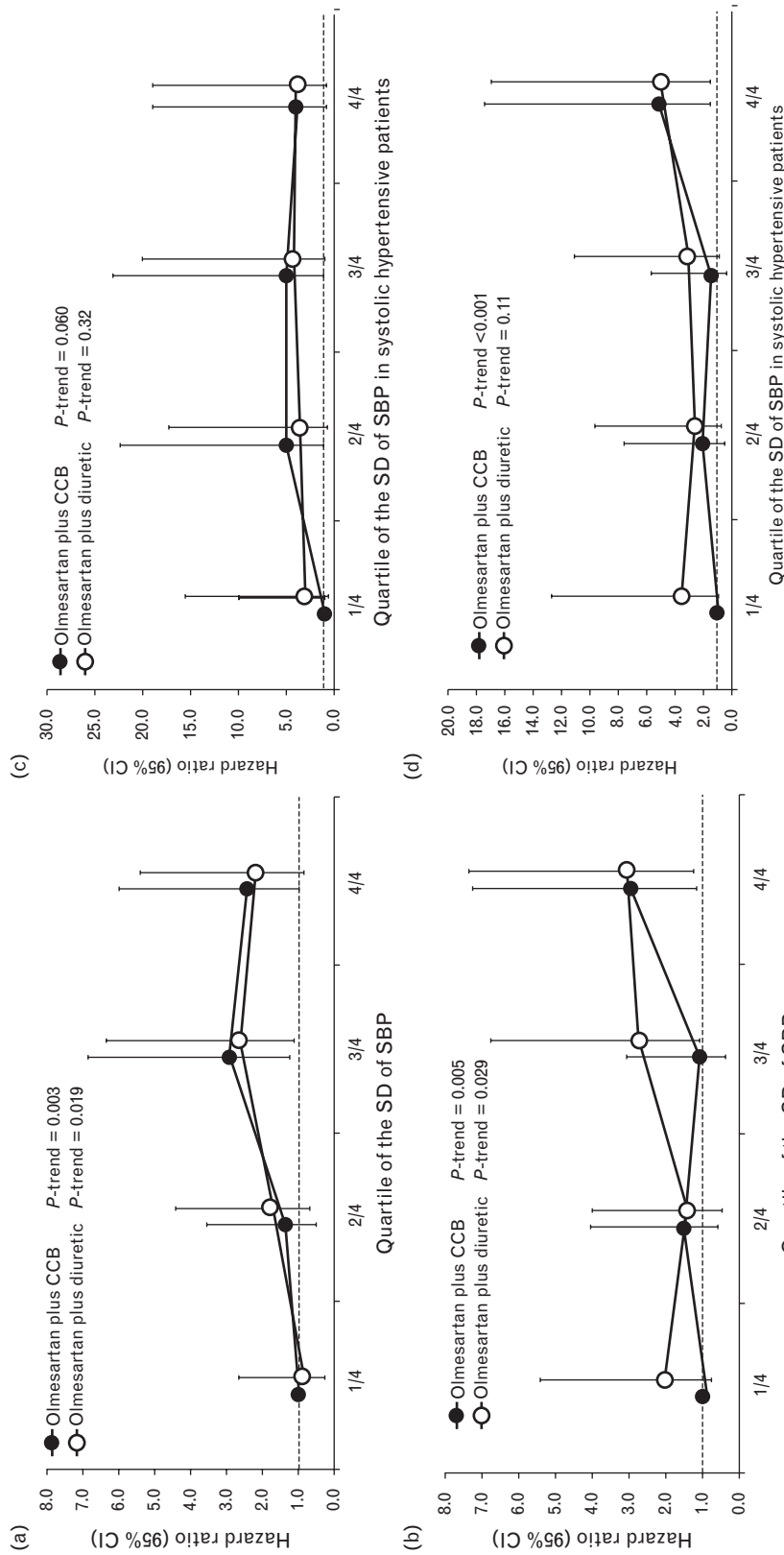


FIGURE 2 Association between the SD of SBP and the hazard ratio for the primary endpoint in the olmesartan along with CCB group and the olmesartan along with diuretic group. (a) Elderly patients, (b) very elderly patients, (c) elderly patients with isolated systolic hypertension, and (d) very elderly patients with isolated systolic hypertension. Elderly, 65–74 years; very elderly, 75–84 years. CCB, calcium channel blocker; CI, confidence interval; SD, standard deviation.

three-factor interaction with SD of SBP*age*treatment was statistically significant when we examined SDIM ($P=0.045$ for hard endpoints, $P=0.043$ for stroke) and peak size ($P=0.033$ for hard endpoints, $P=0.040$ for stroke) instead of SD as VVV metrics.

As the differences in variability between the two age groups can be explained by the higher prevalence of isolated systolic hypertension (ISH) in the very elderly group, we further analyzed whether the differences in the SD of SBP remain between two age groups in the subgroup of ISH. The differences in the SD of SBP between elderly and very elderly were statistically significant in ISH patients but not in non-ISH patients (Table 2). Association between the SD of SBP and the hazard ratio for the primary endpoint was significant in both elderly and very elderly groups (Fig. 1b). Furthermore, the SD of SBP was smaller in olmesartan along with CCB than that in olmesartan along with diuretic both in the elderly and very elderly patients with ISH but not in non-ISH patients (Table 2). Association between the SD of SBP and the hazard ratio for the primary endpoint was significant in the olmesartan along with CCB group among very elderly patients but not significant in other groups (Fig. 2c and d).

DISCUSSION

In this subanalysis of the COLM trial, we demonstrated that VVV of SBP was significantly smaller in the olmesartan along with CCB group compared with those in the olmesartan along with diuretic group among very elderly patients and ISH patients. In addition, when patients were stratified according to the quartiles of SD of SBP, very elderly patients from the olmesartan along with CCB group tended to be clustered in the lower quartiles and those from the olmesartan along with diuretic group tended to be clustered in the higher quartiles, whereas this difference was not noted for elderly patients.

The prevalence of hypertension is well known to increase with age, and many studies have shown a positive correlation between increased BP and cardiovascular mortality or morbidity in elderly hypertensive patients, as well as in younger patients [16–18]. In addition, providing antihypertensive treatment for elderly hypertensive patients has been shown to significantly reduce all-cause mortality, death from cardiovascular disease, and the incidence of cardiovascular disease [1]. Furthermore, the Hypertension in the Very Elderly Trial (HYVET) showed that the incidence of cardiovascular disease and all-cause mortality was also significantly reduced by antihypertensive treatment even in very elderly hypertensive patients [19].

In elderly hypertensive patients, a CCB, an ARB or ACE inhibitor, and a low-dose diuretic are recommended as first-line antihypertensive agents, whereas combination therapy with any two of these drugs is recommended if the BP cannot be controlled by monotherapy [2], based on the results of clinical trials of combination therapy in elderly [5–7]. However, there are few studies elucidating desirable combination therapy for elderly hypertensive patients.

Recently, there have been a number of reports that VVV of BP is a significant and independent risk factor for cardiovascular events such as stroke [12–14,20]. Some

studies have investigated the effects of different antihypertensive drug classes on BP-VVV [21,22]. A meta-analysis of 389 clinical trials demonstrated that patients taking a CCB showed significant reduction of VVV of BP [23], and that adding a CCB to other antihypertensive agents significantly reduced VVV of SBP [24]. Comparison of VVV of SBP among participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial showed chlorthalidone and amlodipine are associated with lower VVV of SBP than lisinopril [15]. Moreover, similar to our results, Matsui *et al.* [25] reported that participants treated with olmesartan along with azelnidipine showed lower day-to-day BP variability than participants treated with olmesartan along with hydrochlorothiazide.

Some studies showed that VVV of BP is an independent risk factor for cardiovascular disease in elderly patients [26]. For example, The Washington Heights-Inwood Columbia Aging Project (WHICAP) reported that participants age 65 years or older with greater BP variability have an increased risk of cerebrovascular disease [27]. However, no large-scale prospective clinical trial has investigated VVV of BP or drug class effects on VVV of BP in very elderly patients. Furthermore, to our knowledge, no previous study has compared the clinical impact of VVV of BP between elderly patients and very elderly patients, although a population survey from the Third National Health and Nutrition Examination Survey (NHANES III) reported that age is one of the major determinants of an increase in VVV of BP [28].

Therefore, the present study is the first to demonstrate that larger VVV of SBP is associated with a higher incidence of cardiovascular events in elderly patients, and that VVV of SBP was smaller in olmesartan along with a CCB group than olmesartan along with a diuretic group especially among very elderly group. It is interesting that there was a difference of the drug class effects on VVV of SBP between the very elderly group and the elderly group.

Further studies will be required to fully explain this difference, but the present findings indicated that one mechanism underlying the superiority of olmesartan along with CCB for preventing cardiovascular events in very elderly hypertensive patients or ISH patients could be its effect on VVV of BP [10]. Vascular stiffness is usually higher in very elderly than elderly and in ISH patients than non-ISH patients. Higher vascular stiffness would be a cause of larger cardiovascular risk and higher VVV of SBP. It has been reported that ARB along with CCB reduced vascular stiffness and also reduced home BP variability more effectively than ARB along with diuretic [25,29]. These reports suggest that ARB along with CCB would prevent cardiovascular events more effectively than ARB along with diuretic via reduction of vascular stiffness in association with a reduction of BP variability. This hypothesis is largely validated by our study, especially in very elderly patients and ISH patients. That is a smaller VVV of SBP and a stronger association between the hazard ratio for cardiovascular events and VVV of SBP in the ARB along with CCB group compared with the ARB along with diuretic group.

It would be interesting to conduct stratified analyses of other cohort studies based on age groups, especially targeting very elderly patients, to determine the clinical significance of VVV of BP more precisely. Because reducing VVV

of BP has been recognized as a potential target for improving the prognosis of hypertensive patients, our study may suggest a new direction for antihypertensive treatment in the elderly because we demonstrated that olmesartan along with CCB reduces VVV of SBP in very elderly hypertensive patients.

The present study had several limitations. First, because this study used the prospective, randomized, open-label, blinded-endpoint design, investigators could be affected by nonblinded allocation of treatment to patients who were hospitalized for angina pectoris or heart failure (included in the primary endpoint). However, there were no significant differences of baseline BP and BP reduction between the two treatment groups, so it is unlikely that the main outcomes of this subanalysis were biased by the investigators. Second, the sample size was relatively small and investigation of a larger patient population over a longer period will be needed to confirm our results. Finally, since only Japanese patients with hypertension were enrolled in this study, the results may not be generalizable to other populations. For example, the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial that compared benazepril along with amlodipine or hydrochlorothiazide, the difference in cardiovascular events between the CCB and diuretic arms was not dependent on age groups in contrast to the present study.

In conclusion, VVV of SBP may mediate the preferable effect of combination of ARB along with CCB on cardiovascular events in patients with high vascular stiffness such as very elderly and also ISH patients.

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Clinical Trial Registration-URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00454662.

Conflicts of interest

H.R., T.O., T.S., I.S., S.T., K.S., S.K., J.H., M.O., N.T., and G.K. have actual conflicts of interest to disclose in relation to the presentation; lecture fees and research funding from various pharmaceutical companies in Japan, that market antihypertensive drugs, including Daiichi Sankyo Co., Ltd. T.K. has no conflicts of interest to disclose.

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Reviewer's Summary Evaluation

Reviewer 1

In this article the authors showed that among very elderly subjects the ARB-CCB combination was more effective than the ARB-diuretic combination in reducing visit-to-visit BP variability (VTV) and that the former treatment was more beneficial in preventing cardiovascular (CV) events.

Although these data are interesting and provide a possible mechanistic explanation for the better efficacy of the ARB-CCB combination, they cannot prove a cause-effect relationship between the VTV and CV event reduction. In addition, they are at variance with the results of the ACCOMPLISH study, in which the greater benefit of the ACE-Inhibitor-CCB over the ACE-inhibitor-diuretic combination was not dependent on age.