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Combinations of olmesartan and a calcium channel blocker or a diuretic in elderly hypertensive patients: a randomized, controlled trial[1]

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Objective: The aim of the present study was to compare the cardiovascular effects of olmesartan, an angiotensin II receptor blocker, combined with a calcium channel blocker (CCB) or a diuretic, in a prospective, randomized, open-label, blinded endpoint trial.

Methods: Japanese hypertensive patients aged at least 65 to less than 85 years with SBP at least 140 mmHg and/or DBP at least 90 mmHg with antihypertensive treatment, or SBP at least 160 mmHg and/or DBP at least 100 mmHg without antihypertensive treatment were randomized to receive olmesartan with either a dihydropyridine CCB or a low-dose diuretic. If SBP and/or DBP remained at least 140 and/or at least 90 mmHg, the other antihypertensive drug was added. The primary endpoint was a composite of fatal and nonfatal cardiovascular events. The median follow-up time was 3.3 years.

Results: Blood pressure decreased similarly in both groups. The primary endpoint occurred in 116/2568 patients (4.5%) in the olmesartan plus CCB group and in 135/2573 patients (5.3%) in the olmesartan plus diuretic group [hazard ratio 0.83, 95% confidence interval (CI) 0.65–1.07, $P=0.16$]. Rates of all-cause death and cardiovascular deaths were similar. Among patients aged at least 75 years, the incidence of stroke tended to be lower in the olmesartan plus CCB group than in the olmesartan plus diuretic group (hazard ratio 0.63, 95% CI 0.38–1.02, $P=0.059$, interaction $P=0.019$). Fewer patients in the olmesartan plus CCB group (8.2%, 211/2568) than in the olmesartan plus diuretic group (9.8%, 253/2573; $P=0.046$) experienced serious adverse events.

Conclusion: Despite no significant difference in cardiovascular events, the different safety profiles suggest that the combination of olmesartan and CCB may be preferable to that of olmesartan and diuretic.

Keywords: blood pressure, calcium channel blockers, diuretics, hypertension, olmesartan, randomized controlled trial

Abbreviations: ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; COLM, Combinations of OLMesartan; SAE, serious adverse event

INTRODUCTION

Hypertension is a major risk factor for cardiovascular morbidity and mortality [1]. Tight control of blood pressure (BP) is recommended for the prevention of cardiovascular diseases [2] and often requires combinations of two or more antihypertensive drugs [3]. Current clinical guidelines for the management of hypertension list several combinations of drugs [4–6]. Only a few studies, however, such as the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) [7] and Combination Therapy of Hypertension to Prevent Cardiovascular Events

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The authors' contributions, members of the COLM Study Committees, and the list of investigators are presented in the Appendix.

[1] Some data from this report were presented as a late-breaking clinical trial at the 23rd European Meeting on Hypertension and Cardiovascular Protection (Milan, Italy), 16 June 2013.

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[8] trials, have directly compared the effects of different combinations.

Combinations of an angiotensin II receptor blocker (ARB) and a calcium channel blocker (CCB) or an ARB and a diuretic are widely used to treat hypertension, and both combinations are recommended in clinical guidelines [4–6]. No studies, however, have compared these combinations in terms of preventing cardiovascular disease.

With the aim of addressing this issue, we conducted the Combinations of OLMesartan (COLM) study to compare the effects of an ARB combined with a CCB with those of an ARB combined with a diuretic on cardiovascular endpoints in a high-risk cohort of Japanese elderly hypertensive patients. In this study, we used olmesartan as the ARB in both groups because it had good antihypertensive effects in several large-scale, international clinical trials [9–13].

METHODS

Study design

The rationale, study design, and implementation of the COLM study are described in more detail in our previous report [14]. This multicentre prospective, randomized, open-label blinded-endpoint trial was conducted between April 2007 and September 2011 at 707 primary care and cardiology centres in Japan. Patient recruitment was completed in September 2008. After randomization, all patients were followed up for at least 3 years until the trial was terminated at the prespecified time. The trial was conducted in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by institutional review boards at each participating centre.

Patients

Hypertensive patients aged at least 65 to less than 85 years with a history of cardiovascular disease or risk factors for cardiovascular disease, including diabetes mellitus or dyslipidemia, were eligible for the study. Patients were enrolled if their clinic-measured SBP was at least 140 mmHg and/or their DBP was at least 90 mmHg during treatment with one or more antihypertensive drugs at enrolment, or if their SBP was at least 160 mmHg and/or DBP was at least 100 mmHg without antihypertensive treatment. All patients provided written informed consent.

Randomization and treatments

Patients were randomized 1 : 1 using a dynamic allocation method with stratification for sex, age ($\geq$75/<75 years), history of cardiovascular disease, BP (mild/moderate or severe hypertension according to the Japanese guideline for the management of hypertension [15]), prior use of antihypertensive agents, and centre. Randomization was conducted using a computerized system by the COLM study data centre, and the random allocation sequence was concealed until the end of the enrolment period. Patients were treated with olmesartan (5–40 mg/day) and either a long-acting dihydropyridine CCB [amlodipine (2.5 or 5 mg/day) or azelnidipine (8 or 16 mg/day)] or a low-dose diuretic (trichlormethiazide $\leq$1 mg, hydrochlorothiazide $\leq$12.5 mg, or indapamide $\leq$1 mg and other diuretics). Wherever possible, low doses of diuretics were preferred [16]. Medication was administered orally, once a day, usually after breakfast. The choice of which CCB and diuretic were used concomitantly with olmesartan was at the discretion of the investigator in charge of each patient [14].

Study protocol

The target SBP and DBP were less than 140 and less than 90 mmHg, respectively, in both groups. For patients with BP exceeding these targets, the dose of each drug was to be increased. If the target BP was not achieved with maximal doses of the allocated drug, the other class of antihypertensive drug was added, followed by the addition of other antihypertensive drugs, including β-blockers, α-blockers, and angiotensin-converting enzyme (ACE) inhibitors. If the BP decreased excessively, the doses of antihypertensive agents other than the study drugs were reduced, or the other drugs were discontinued with the aim of continuing the combination for as long as possible [14].

Outcomes

Measurement of BP, assessment of cardiovascular events, and laboratory tests were conducted at 1, 3, and 6 months after randomization, and then every 6 months thereafter. BP was measured at least twice at intervals of 1–2 min, and the mean value of two stable measurements that differed by less than 5 mmHg was used. The primary endpoint was a composite of fatal and nonfatal cardiovascular events. Cardiovascular events included sudden death; new occurrence or recurrence of cerebral infarction, cerebral haemorrhage, subarachnoid haemorrhage, or transient ischaemic attack; new occurrence or recurrence of myocardial infarction; coronary revascularization (percutaneous intervention or coronary artery bypass grafting); hospitalization for angina pectoris or heart failure; and renal events (doubling of serum creatinine, serum creatinine $\geq$2.0 mg/100 ml, and end-stage renal disease).

Secondary endpoints included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke except transient ischaemic attack, all-cause deaths, composite of hard endpoints (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke except transient ischaemic attack), new-onset diabetes, incidence of specific events (sudden death, cerebrovascular events, cardiac events, and renal events), new occurrence of atrial fibrillation, adverse events, and the proportion of patients who withdrew from the allocated treatment. Adverse events, classified as drug-related or nondrug-related and serious or nonserious, were monitored throughout the study. All events contributing to the primary and secondary endpoints and all serious adverse events (SAEs) reported by the participating physicians were adjudicated by the Endpoint Committee, which was blinded to the study group.

Sample size

The rationale for the sample size is reported elsewhere [14]. Briefly, the incidence of cardiovascular events (i.e., the primary endpoint) was estimated to be 2% per year, and the relative difference in the incidence of cardiovascular events between the two groups was estimated to be 33%. Therefore, more than 2000 patients were needed for each

group to provide a significance level of 5% (two-sided) at a power of 80%.

Statistical methods

All analyses were conducted according to the intention-to-treat principle. Time-to-event curves for cardiovascular events were plotted using the Kaplan–Meier method. Stratified log-rank tests were conducted with sex, age, and history of cardiovascular disease as strata. Hazard ratios and 95% confidence intervals (CIs) were calculated using the stratified proportional hazards model. Exploratory analyses of prespecified subgroup analyses were conducted, and interactions between treatment group and each subgroup were investigated. Patient characteristics at baseline, BP at the end of the trial, and the frequency of adverse events between two groups were compared using the *t*-test (for continuous variables) and Fisher's exact test (for categorical variables). The *t*-test was used to compare the change in BP, and the analysis of covariance adjusted by baseline data was conducted to compare the average change in heart rate between two groups. Two interim analyses were planned to either continue or discontinue the study on the basis of ethical and scientific considerations, with adjustment for repeated comparisons using the O'Brien–Fleming α-spending function, and the results were evaluated by the Independent Data Monitoring Committee. The prespecified significant levels for stopping criteria were 0.00001 for the first interim analysis and 0.003 for the second interim analysis. If these were met, the Data Monitoring Committee would ask the Steering Committee to either amend the study protocol or discontinue the study. For the primary endpoint, the significance level for the final analysis was set at 0.049 (two-sided) considering the two interim analyses. In other analyses, the level of significance was 0.05 (two-sided). All statistical analyses were done using SAS 9.1 (SAS Institute, Inc., Cary, North Carolina, USA).

RESULTS

Patients

Of 5658 patients assessed for eligibility, 489 patients met the exclusion criteria and 28 patients withdrew consent before enrolment. Therefore, 5141 patients were randomized. Overall, 46 patients in the olmesartan plus CCB group and 72 patients in the olmesartan plus diuretic group were lost to follow-up, leaving 2568 and 2573 patients in these groups, respectively (Fig. 1). The results of two interim analyses in October 2009 and December 2010 did not meet the prespecified early stopping criteria. The median follow-up period was 3.3 years (range 1 day to 4.3 years), and the follow-up rate was 98.0%. The baseline characteristics, including BP at randomization, are shown in Table 1. The mean age of patients was 73.6 years, and 51.6% were men. There were no significant differences in baseline characteristics between the two groups. Approximately 24% of patients had a history of cardiovascular diseases, including stroke (14.6%) and ischaemic heart disease (11.0%). Approximately 81% of patients were treated with antihypertensive agents at enrolment; the most common types were ARBs (49%) and CCBs (37%).

At 3 years, the mean number of antihypertensive drugs used, including the allocated drugs, was 2.1 in the olmesartan plus CCB group and 2.1 in the olmesartan plus diuretic group ($P = 0.64$). The median number of drugs was two in both groups.

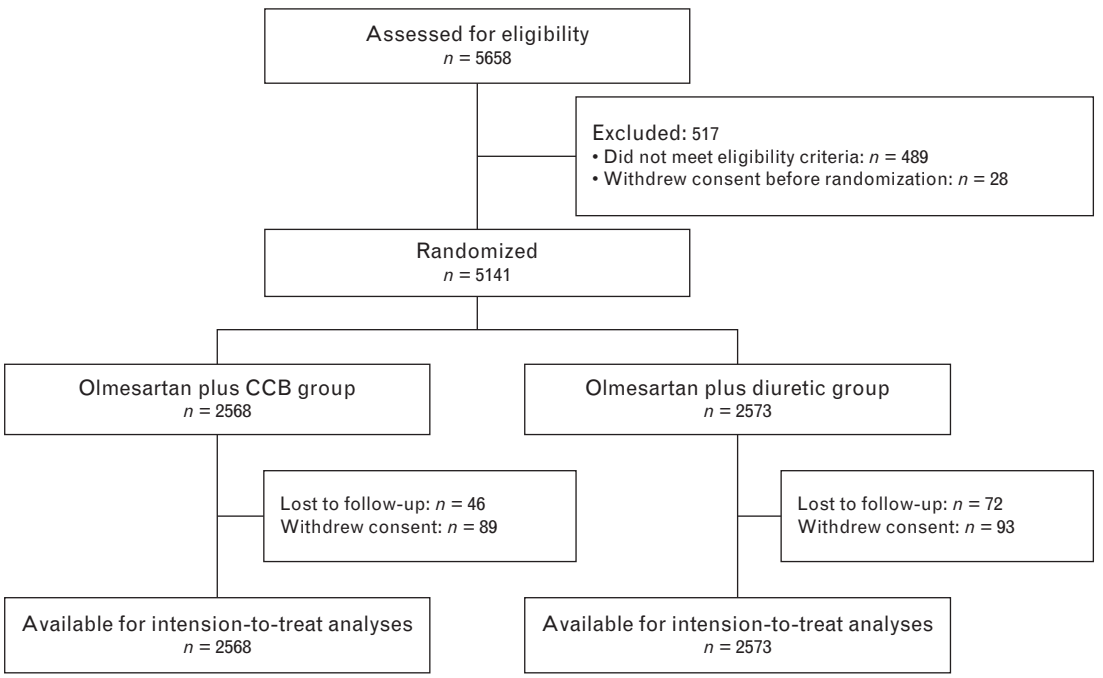

FIGURE 1 Patient disposition.

TABLE 1. Baseline characteristics of the study population according to treatment group

Characteristic	Olmesartan plus CCB ($n=2568$)	Olmesartan plus diuretic ($n=2573$)	*P*-Value
Sex			
Men	1323 (51.5)	1330 (51.7)	0.91
Women	1245 (48.5)	1243 (48.3)	
Age (years)	73.6 ± 5.3	73.6 ± 5.4	0.74
≥75 years old	1109 (43.2)	1114 (43.3)	0.95
<75 years old	1459 (56.8)	1459 (56.7)	
BMI (kg/m^2)	24.3 ± 3.5	24.2 ± 3.4	0.26
eGFR (ml/min per 1.73 m^2)	67.6 ± 19.0	67.3 ± 18.3	0.62
SBP (mmHg)	158.0 ± 12.7	158.0 ± 12.5	0.96
DBP (mmHg)	87.1 ± 10.8	86.9 ± 10.8	0.58
Heart rate (bpm)	73.1 ± 9.9	72.9 ± 9.3	0.49
Cardiovascular history			
Stroke	369 (14.4)	382 (14.9)	0.63
Ischaemic heart disease	286 (11.1)	277 (10.8)	0.68
Cardiovascular risk factors			
Dyslipidemia	1165 (45.5)	1172 (45.8)	0.84
Diabetes mellitus	684 (26.6)	678 (26.4)	0.82
Smoking	641 (25.1)	648 (25.4)	0.84
Drinking	1090 (42.8)	1086 (42.5)	0.88
Use of antihypertensive drugs at enrolment[a]			
ARB	1262 (49.2)	1254 (48.9)	0.84
CCB	977 (38.1)	916 (35.8)	0.08
β-Blockers	231 (9.0)	191 (7.5)	0.04
ACE inhibitors	149 (5.8)	154 (6.0)	0.76
Diuretics	146 (5.7)	168 (6.6)	0.20
α-Blockers	71 (2.8)	70 (2.7)	1.00
Concomitant use of other drugs			
Statin	704 (27.5)	719 (28.1)	0.64
Antiplatelet drugs	555 (21.7)	561 (21.9)	0.83
Antidiabetic drugs	472 (18.4)	497 (19.4)	0.37

Data are *n* (%) or mean ± standard deviation. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; eGFR: estimated glomerular filtration rate, calculated using the Japanese formula $194 \times Cr - 1.094 \times age - 0.287$ (×0.739 for women).
[a]Excludes 16 patients for whom data were not collected after randomization ($n=2563$ in the olmesartan plus CCB group, $n=2562$ in the olmesartan plus diuretic group).

The following drugs were used in the olmesartan plus CCB group: amlodipine (44.9%) and azelnidipine (49.8%), and in the olmesartan plus diuretic group: trichlormethiazide (62.4%), indapamide (22.8%), hydrochlorothiazide (2.3%), and other thiazides (3.5%). The mean doses of olmesartan were 18.3 ± 8.1 and 18.5 ± 8.6 mg/day for patients in the olmesartan plus CCB and olmesartan plus diuretic groups, respectively.

Blood pressure and heart rate

BP at baseline was approximately 158/87 mmHg, and was similar in both groups (Table 1). The time-course of changes in SBP and DBP was similar in both groups (Fig. 2). At the end of the trial, the mean SBP/DBP was 132.9 ± 12.6/73.2 ± 9.8 mmHg in the olmesartan plus CCB group and 132.9 ± 13.6/73.5 ± 9.8 mmHg in the olmesartan plus diuretic group, corresponding to mean reductions in SBP/DBP of 24.4 ± 16.4/13.8 ± 12.0 and 24.9 ± 17.3/13.7 ± 12.4 mmHg ($P=0.30/0.79$), respectively. There were no significant differences in mean SBP or DBP at each visit between the two groups.

Overall, 69.2% (1735/2568) of patients in the olmesartan plus CCB group and 70.5% (1759/2573) of patients in the olmesartan plus diuretic group ($P=0.30$) achieved the target BP levels (SBP <140 mmHg and DBP <90 mmHg).

Heart rate was 73.1 and 72.9 bpm ($P=0.49$) at baseline in the olmesartan plus CCB and olmesartan plus diuretic groups, respectively, and decreased slightly to 69.7 ± 11.2 and 70.5 ± 11.7 bpm, respectively, at 3 years. The decrease in heart rate was significantly greater in the olmesartan plus CCB group than in the olmesartan plus diuretic group ($P=0.01$), with a mean difference of 0.55 bpm.

Primary outcome

Kaplan–Meier analysis of the time to the first primary endpoint is shown in Fig. 3. The incidence and hazard ratio of the primary endpoint are shown in Fig. 4. The primary endpoint occurred in 116/2568 patients (4.5%) in the olmesartan plus CCB group, and in 135/2573 patients (5.3%) in the olmesartan plus diuretic group (hazard ratio 0.83, 95% CI 0.65–1.07, $P=0.16$). The incidence of the primary endpoint per 1000 patient-years was 14.8 in the olmesartan plus CCB group and 17.6 in the olmesartan plus diuretic group. There were no significant differences in the rates of each type of event between the two groups (Fig. 4).

Secondary and other prespecified endpoints

Overall, 64/2568 patients (2.5%) in the olmesartan plus CCB group (8.0/1000 patient-years) and 76/2573 patients (3.0%) in the olmesartan plus diuretic group (9.7/1000 patient-years) died during the study (hazard ratio 0.83, 95% CI 0.59–1.15, $P=0.27$). The rates of all-cause death and cardiovascular death were not significantly different between the two groups. The composite of hard endpoints occurred in 72/2568 patients (2.8%) in the olmesartan plus CCB

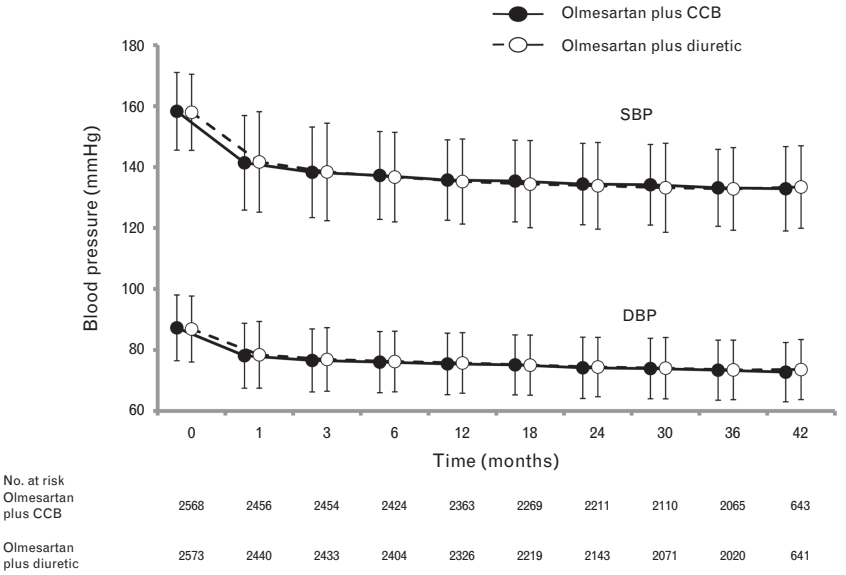

FIGURE 2 Time-course of changes in blood pressure.

group and in 88/2573 patients (3.4%) in the olmesartan plus diuretic group (hazard ratio 0.80, 95% CI 0.58–1.09, $P=0.16$). The rates of new-onset atrial fibrillation and diabetes were not significantly different between the two groups (Fig. 4).

Table 2 shows the results of prespecified subgroup analyses. The incidence rates of the primary endpoint among older patients (≥75 years old), in patients without diabetes, and in patients without dyslipidemia were lower in the olmesartan plus CCB group than in the olmesartan plus diuretic group; however, the interactions were not statistically significant.

Among older patients (≥75 years old), the incidence of the composite of hard endpoints was also lower in the olmesartan plus CCB group than in the olmesartan plus diuretic group (hazard ratio 0.64, 95% CI 0.42–0.97, $P=0.03$), although the interaction was not significant ($P=0.12$). In this subgroup, the incidence of stroke was also lower in the olmesartan plus CCB group (hazard ratio 0.63, 95% CI 0.38–1.02, $P=0.059$) and the interaction between treatment and age subgroup was statistically significant ($P=0.019$).

Safety and adverse events

A total of 77/2568 patients (3.0%) in the olmesartan plus CCB group and 131/2573 patients (5.1%) in the olmesartan plus diuretic group ($P<0.001$) were withdrawn because of SAEs. The incidence of SAEs was lower in the olmesartan plus CCB group (211/2568 patients, 8.2%) than in the olmesartan plus diuretic group (253/2573 patients, 9.8%) ($P=0.046$). The three most frequent SAEs were malignancy (olmesartan plus CCB vs. olmesartan plus diuretic: 2.5 vs.

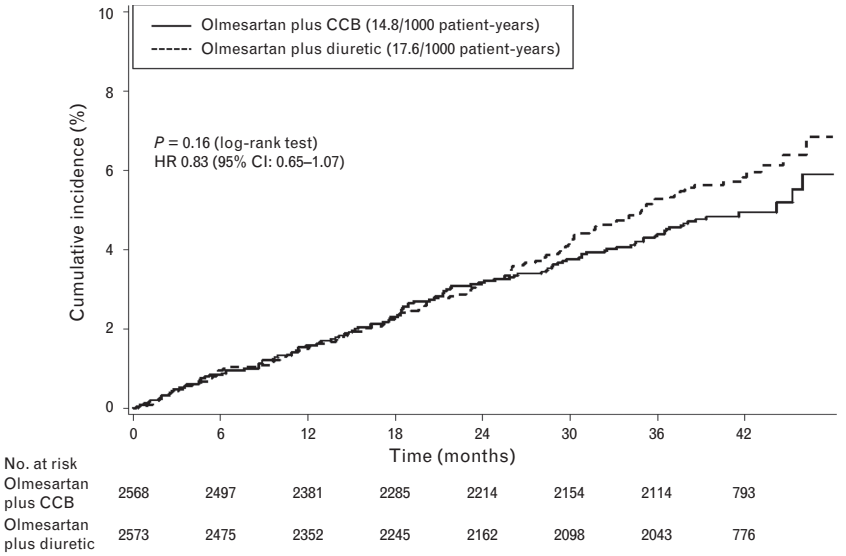

FIGURE 3 Kaplan–Meier curves for the primary composite endpoint of fatal and nonfatal cardiovascular events.

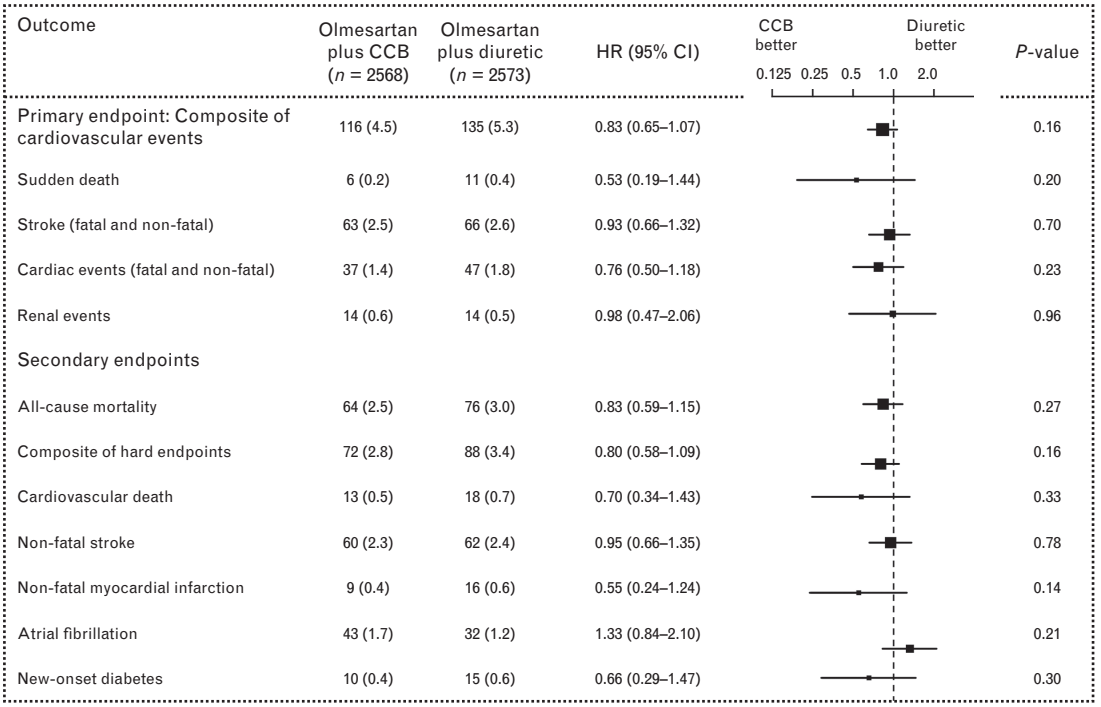

FIGURE 4 Incidence rates and hazard ratios of the primary composite endpoint, of individual components of the primary endpoint, and of the secondary endpoints. The hazard ratios and 95% CIs were determined using a stratified Cox proportional hazards model taking into account sex, age, and baseline cardiovascular disease. The *P*-values were derived from a log-rank test, stratified by sex, age, and baseline cardiovascular disease. CCB, calcium channel blocker; CI, confidence interval.

TABLE 2. Results of prespecified subgroup analyses for the primary endpoint

Subgroup	Olmesartan plus CCB ($n = 2568$)	Olmesartan plus diuretic ($n = 2573$)	Hazard ratio (95% CI)	*P*-Value	*P*-Value (interaction)
Sex					
Men	63/1323 (4.8)	76/1330 (5.7)	0.82 (0.58–1.14)	0.24	0.81
Women	53/1245 (4.3)	59/1243 (4.7)	0.87 (0.60–1.26)	0.46	
Age					
<75 years old	58/1459 (4.0)	55/1459 (3.8)	1.03 (0.71–1.49)	0.85	0.14
≥75 years old	58/1109 (5.2)	80/1114 (7.2)	0.70 (0.50–0.99)	0.04	
BMI					
<25 (kg/m^2)	76/1525 (5.0)	93/1527 (6.1)	0.81 (0.59–1.09)	0.17	0.74
≥25 (kg/m^2)	40/1022 (3.9)	41/1018 (4.0)	0.94 (0.60–1.45)	0.78	
eGFR					
<60 ml/min per 1.73 m^2	43/622 (6.9)	52/642 (8.1)	0.82 (0.55–1.24)	0.35	0.94
≥60 ml/min per 1.73 m^2	47/1230 (3.8)	55/1224 (4.5)	0.83 (0.56–1.23)	0.37	
Diabetes mellitus					
Yes	48/684 (7.0)	42/678 (6.2)	1.12 (0.74–1.69)	0.58	0.06
No	68/1884 (3.6)	93/1895 (4.9)	0.71 (0.52–0.97)	0.03	
Dyslipidemia					
Yes	68/1165 (5.8)	66/1172 (5.6)	1.01 (0.72–1.41)	0.94	0.08
No	48/1398 (3.4)	69/1390 (5.0)	0.68 (0.47–0.98)	0.03	
History of cardiovascular disease					
Yes	55/610 (9.0)	59/615 (9.6)	0.90 (0.62–1.30)	0.58	0.61
No	61/1958 (3.1)	76/1958 (3.9)	0.78 (0.56–1.10)	0.16	

Data are *n* of patients reaching the primary endpoint/total *n* (%). CCB, calcium channel blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate.

3.1%; $P = 0.17$), gastrointestinal disorders (1.1 vs. 1.1%; $P = 0.79$), and infection (0.9 vs. 0.9%; $P = 0.76$). New-onset diabetes occurred in 10 patients (0.4%) in the olmesartan plus CCB group and 15 patients (0.6%) in the olmesartan plus diuretic group (hazard ratio 0.66, 95% CI 0.29–1.47, $P = 0.30$). Regarding laboratory events, the incidence of hyperuricaemia was greater in the olmesartan plus diuretic group than in the olmesartan plus CCB group (6.5 vs. 2.6%, $P < 0.001$).

DISCUSSION

Over a median follow-up period of 3.3 years, there were no differences in the cardiovascular risk reduction conferred

using olmesartan, an ARB, in combination with either a CCB or a diuretic. The incidence of SAEs, however, was significantly lower in the olmesartan plus CCB group than in the olmesartan plus diuretic group. Patients in the present study were well matched in terms of age, obesity, history of cardiovascular disease, cardiovascular risk factors, and antihypertensive medications. BP at baseline and 3 years were similar in both groups, with comparable reductions in BP in both groups.

Several studies have examined the effects of combinations of antihypertensive drugs with different mechanisms of action. For example, the ACCOMPLISH trial showed that the combination of an ACE inhibitor and a CCB was superior to that of an ACE inhibitor and a diuretic for preventing cardiovascular events [7], and the Combination Therapy of Hypertension to Prevent Cardiovascular Events trial showed that the combination of a CCB and a diuretic was superior to that of a CCB and a β-blocker [8]. Among studies examining the efficacy of add-on antihypertensive drugs, the Losartan Intervention For Endpoint reduction in hypertension study showed that an ARB-based regimen with an add-on diuretic was superior to a β-blocker–based regimen with an add-on diuretic for preventing cardiovascular events [17], whereas the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm showed that a CCB-based regimen with an add-on ACE inhibitor was superior to a β-blocker–based regimen with an add-on diuretic [18]. The results of these two studies suggested that the combination of an ARB and a diuretic or a CCB and an ACE inhibitor had some advantages over that of a β-blocker and a diuretic for treating hypertension. In the present study, we compared two widely used combinations of hypertensive drugs: an ARB and a CCB, and an ARB and a diuretic.

The primary endpoint, a composite of cardiovascular morbidity and mortality, and its individual components were not significantly different between the two groups in our study, indicating that both combinations conferred similar reductions in cardiovascular risk in elderly hypertensive patients, consistent with earlier studies showing that BP lowering is essential to reduce cardiovascular morbidity and mortality in hypertensive patients [19–21]. Although the present results do not support the conclusion of the ACCOMPLISH trial [7] that the combination of a renin–angiotensin system (RAS) inhibitor and a CCB is superior to that of a RAS inhibitor and diuretic, we could not consider a smaller relative risk reduction such as 19.6% in the ACCOMPLISH trial, because the present study was specifically powered to detect a relative risk reduction of 33% between the two groups [14]. Nevertheless, the reason why the present results do not support those of the ACCOMPLISH trial may be differences in the races of study patients and the use of an ACE inhibitor vs. an ARB. The higher salt sensitivity in the older Japanese patients (mean age: 73.6 years) in our study than that in the slightly younger predominantly white (83.5%) (mean age: 68.4 years) patients in the ACCOMPLISH trial may have caused greater efficacy of the combination of the RAS inhibitor and diuretic in our study relative to theirs. Another important issue is that stroke was the most common component of the primary endpoint (51.4%) in our study, whereas myocardial infarction (23.1%) and coronary revascularization (58.5%) were more common in the ACCOMPLISH trial. The different pattern of endpoints between the two trials may be related to differences in ethnicity and the severity of cardiac risk at enrolment. It is well known that the incidence of stroke is more strongly associated with BP than is myocardial infarction. Indeed, the two groups in our study achieved similar SBP with a similar incidence of stroke. Although the incidence of the primary endpoint was not significantly different between the two groups, the prespecified subgroup analyses showed that the incidence of stroke among patients aged at least 75 years tended to be lower in the olmesartan plus CCB group ($P = 0.059$), with a statistically significant interaction ($P = 0.019$), which should be confirmed in future studies.

There were more SAEs and also SAEs that required treatment discontinuation in the olmesartan plus diuretic group than in the olmesartan plus CCB group. Furthermore, hyperuricaemia was more common in the olmesartan plus diuretic group, even though low doses of diuretics were used. On the basis of these tolerability issues, we suggest that the combination of an ARB and CCB may be preferable to that of an ARB and diuretic for elderly hypertensive patients.

Guidelines for the treatment of hypertension currently recommend target SBP/DBP less than 140/less than 90 mmHg for general hypertensive patients [4–6]. To achieve such targets, it is often necessary to use multiple antihypertensive drugs of different classes. Consequently, numerous clinical trials have used two or more antihypertensive drugs [21,22]. In recent years, various combination antihypertensive drugs have been launched, and fixed combinations of two antihypertensive drugs are now widely used in clinical practice. In the United States, the combination of a RAS inhibitor and a diuretic or a CCB is the preferred one, whereas that of a CCB and β-blocker or a diuretic is an acceptable one [23]. These recommendations, however, are not fully supported by clinical evidence. Therefore, further studies are necessary to provide adequate clinical evidence to either support or change the current clinical recommendations. Additionally, it will also be necessary to determine the safety profiles and cardiovascular risk reduction associated with the use of other ARBs in combination with a β-blocker, CCB, or diuretic.

Some limitations warrant mention. First, we used the method of prospective, randomized, open-label blinded-endpoint trial, which may lead to some investigator bias. Because BP control was similar in both groups, however, it is unlikely that some investigator bias affected the main outcomes of this study. Regarding statistical power, the incidence of the primary endpoint was close to the expected incidence. Because the sample size was designed to detect a relative difference of 33%, however, more patients were necessary to detect the smaller than expected difference in the incidence of the primary endpoint. Another limitation is that we only enrolled Japanese elderly hypertensive patients, so the results may not be generalizable to other populations.

In conclusion, antihypertensive drugs are widely prescribed to reduce the risk of serious cardiovascular events in patients deemed to be at high risk of such events. The

current clinical guidelines for the management of hypertension advocate the use of multiple antihypertensive drugs in combination to help reach BP targets. Although there is abundant evidence supporting the use of combination therapy, very few studies have compared different combinations of drugs. We found no marked differences in the cardiovascular risk reduction by using olmesartan together with either a CCB or a diuretic. When considering the safety aspects, however, a regimen consisting of olmesartan and a CCB may be preferable to olmesartan in combination with a diuretic. Well designed studies are needed to compare the cardiovascular risk reduction profiles and safety profiles of combination regimens based on an ARB, ACE inhibitor, or CCB.

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Conflicts of interest

T.O., T.S., H.R., I.S., K.Shimamoto., H.M., K.Shimada, S.I., M.H., T.I., S.T., J.H., S.K., G.K., N.U., K.H., M.O., N.T., T.I., S.U., N.K., and S.T. have received travel expenses, payment for speaking at meetings, or funding for research from one or more pharmaceutical companies that market antihypertensive drugs, including Daiichi Sankyo Co. Ltd. S.M. has no conflicts of interest to disclose.

Appendix

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Reviewer's Summary Evaluation

Reviewer 1

For decades the investigation of the treatment of arterial hypertension in randomized controlled trials has consisted of the theoretical comparison of two monotherapies to which later on and if required one, two, or more drugs were added in a nonrandomized way. In many of those studies different combination therapies were used during the trial coming to complicate the final conclusions of those trials. The present study compares two combinations using olmesartan as a common drug that combines either with a diuretic or with a calcium cannel blocker. This type of study design initiated with the ACCOMPLISH study is, in my opinion, the most adequate to test the capacity of what the great majority of patients with arterial hypertension require for the control of BP, combination therapy.