The Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure: COACH, a Randomized, Double-Blind, Placebo-Controlled, 8-Week Factorial Efficacy and Safety Study

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ABSTRACT

Background: Hypertension guidelines recommend the use of 2 agents having complementary mechanisms of action when >1 agent is needed to achieve blood pressure (BP) goals.

Objective: The aim of this study was to compare the efficacy and tolerability of combinations of olmesartan medoxomil (OM) and amlodipine besylate with those of the component monotherapies in patients with mild to severe hypertension.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled, factorial study. Patients who were naive to antihypertensive therapy or who underwent a washout of previous antihypertensive therapy for up to 2 weeks and had a seated diastolic BP (SeDBP) of 95 to 120 mm Hg were randomized to receive 1 of the following for 8 weeks: OM 10, 20, or 40 mg; amlodipine (AML) 5 or 10 mg; each possible combination of OM and AML; or placebo. The primary end point was the change from baseline in SeDBP at week 8, with secondary end points including the change in seated systolic blood pressure (SeSBP), the proportion of patients reaching the BP goal (<140/90 mm Hg; <130/80 mm Hg for patients with diabetes), and the proportions of the intention-to-treat population reaching BP thresholds of <120/80, <130/80, <130/85, and <140/90 mm Hg. Safety and tolerability were also evaluated, with a particular focus on the incidence and severity of edema.

Results: Of the 1940 randomized patients, 54.3% were male. The mean age of the study population was 54.0 years and 19.8% were aged ≥65 years. The mean baseline BP was 164/102 mm Hg, and 79.3% of patients had stage 2 hypertension. Combination therapy with OM and AML was associated with dose-dependent reductions in SeDBP (from −13.8 mm Hg with OM/AML 10/5 mg to −19.0 mm Hg with OM/AML 40/10 mg) and SeSBP (from −23.6 mm Hg with OM/AML 20/5 mg to −30.1 mm Hg with OM/AML 40/10 mg) that were significantly greater than the reductions with the corresponding component monotherapies ($P < 0.001$). At week 8, the number of patients achieving the BP goal ranged from 57 of 163 (35.0%) to 84 of 158 (53.2%) in the combination-therapy groups, from 32 of 160 (20.0%) to 58 of 160 (36.3%) in the OM monotherapy groups, and from 34 of 161 (21.1%) to 53 of 163 (32.5%) in the AML monotherapy groups ($P < 0.005$, combination therapies vs component monotherapies), compared with 14 of 160 (8.8%) in the placebo group. Achievement of the BP thresholds was highest in the combination-therapy groups, with 56.3% and 54.0% of patients achieving a BP <140/90 mm Hg with OM/AML 20/10 and 40/10 mg, respectively. Combination therapy was generally well tolerated, and no unexpected safety concerns emerged in the course of the study. The most common adverse events were edema (ranging from 9.9% [OM 20 mg] to 36.8% [AML 10 mg], compared with 12.3% with placebo) and headache (ranging from 2.5% [OM/AML 10/5 mg] to 8.7% [OM 20 mg], compared with 14.2% with placebo).

Conclusion: The combination of OM and AML was effective and well tolerated in this adult population with hypertension. (*Clin Ther.* 2008;30:587–604) © 2008 Excerpta Medica Inc.

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Key words: hypertension, olmesartan medoxomil, amlodipine besylate, fixed-dose combination, edema.

INTRODUCTION

According to data from the most recent National Health and Nutrition Examination Survey (2003–2004),[1] the age-adjusted prevalence of hypertension in the US population is 30% and increasing. Although improved from the previous survey (2001–2002), attainment of blood pressure (BP) control (BP <140/90 mm Hg) remains low (36.8%).[1] The increased prevalence of hypertension appeared to be driven by a disproportionate increase in prevalence and poor BP control among women[2] and Mexican Americans.[1] A meta-analysis of 61 prospective, observational studies enrolling a total of 1 million adults indicated that for every 2–mm Hg decrease in systolic BP (SBP), there was a 7% reduction in the risk of cardiovascular mortality and a 10% reduction in the risk of stroke mortality.[3] Moreover, it has been estimated that controlling BP to the levels recommended in current guidelines would prevent 370,000 coronary events in men and 150,000 coronary events in women over 10 years.[4]

One of the main reasons for poor BP control has been the reluctance of physicians to intensify antihypertensive therapy in patients who have not reached their BP goal.[5] Large trials have found that BP goals can be achieved in most patients with hypertension; however, the majority of patients will require ≥2 antihypertensive agents.[6–10] Both US and European guidelines recommend that physicians consider starting therapy with 2 agents in patients who are at high cardiovascular risk or who have a BP >20/10 mm Hg above goal.[11,12] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[11] (JNC 7) recommends that drug combinations be used, if indicated, as initial therapy for most patients with stage 2 hypertension (SBP ≥160 mm Hg or diastolic BP [DBP] ≥100 mm Hg) to accelerate achievement of BP targets, as well as to avoid multiple drug-titration steps and multiple patient visits.

When contemplating combination therapy, the use of antihypertensive agents having different mechanisms of action may augment overall BP-lowering effects.[11] Furthermore, the actions of one agent may ameliorate the adverse effects of another. For example, dihydropyridine calcium channel blockers (CCBs) are potent vasodilators and are intrinsically natriuretic, inducing a state of negative sodium balance[13] and leading to stimulation of the renin–angiotensin–aldosterone system (RAAS); on the other hand, drugs such as angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors block the RAAS and, when used in combination with a CCB, reinforce the antihypertensive effects of the CCB.[14] Peripheral edema, one of the adverse events most commonly associated with dihydropyridine CCBs, is likely to result from preferential arteriolar vasodilatation and an increase in the pressure gradient between the arteriolar and venular capillaries, leading to exudation of interstitial fluid.[15,16] This effect may be ameliorated by concomitant administration of ARBs or ACE inhibitors, which lower precapillary resistance, normalize intracapillary pressure, and reduce fluid exudation.[15–18]

Among newer antihypertensive combinations to become available are fixed-dose combinations of an ARB and a dihydropyridine CCB. The combination of olmesartan medoxomil (OM) and amlodipine is indicated for use when initial treatments are ineffective in achieving the BP goal. Combination therapies are often evaluated in studies having a factorial design, in which each dose of monotherapy is compared with each possible combination of these doses. This allows comparison of the efficacy of the combination with that of the individual monotherapy components, with the monotherapies compared with placebo for internal validity.[19]

The Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure (COACH) study was an 8-week factorial study with the objective of assessing the antihypertensive efficacy of the combination of OM and amlodipine (AML) at various doses compared with the respective monotherapy components in patients with mild to severe hypertension. Another objective was to evaluate the safety profile of the combinations relative to monotherapy, with a particular focus on the incidence and severity of edema.

PATIENTS AND METHODS

Study Population

Study participants were recruited from patients presenting to the research sites (primary care practices, specialist practices, hospitals, or research centers). Patients were eligible for randomization if they were aged ≥18 years, had a mean seated DBP (SeDBP) of

95 to 120 mm Hg at both the visit before randomization and the randomization visit, and had a difference of ≤10 mm Hg between the 2 mean SeDBP measurements. Patients with a history of cardiovascular disease or uncontrolled diabetes or who smoked >1 pack of cigarettes per day were excluded. Patients also were excluded if they had an SeDBP >120 mm Hg, had laboratory values or systemic disease considered clinically significant by the investigator, or were taking any medication that could interfere with the objectives of the study.

Study Design

This was an 8-week, randomized, double-blind, factorial study conducted at 172 clinical sites in the United States. The study was conducted in accordance with institutional review board (IRB) regulations, the Declaration of Helsinki, and good clinical practice guidelines. All patients provided written informed consent at screening. All medications were provided to patients free of charge; patients were compensated for travel expenses and time, as approved by the IRB, but received no other compensation.

After the screening visit, eligible patients who had not been taking antihypertensive medications for at least 2 weeks before screening were immediately randomized to receive 1 of the following for 8 weeks: OM monotherapy (10, 20, or 40 mg), AML monotherapy (5 or 10 mg), combination therapy (including all possible combinations of the monotherapy doses of OM and AML), or placebo. Patients who were taking antihypertensive medications at the screening visit entered a washout phase of up to 2 weeks, during which all antihypertensive medications were withdrawn. If patients met the criteria for inclusion after withdrawal of antihypertensive medications, they were randomized to 1 of the 12 groups. Randomization was accomplished by assigning each patient a unique 4-digit number via an interactive voice-response system.

Patients were given 2 weeks' worth of medication at each visit and were instructed to take their medication at the same time each day (±2 hours), except on the day of a visit. Clinic visits were scheduled for 2, 4, 6, and 8 weeks after randomization. Patients who did not return for a scheduled clinic visit received telephone and mail follow-ups, including certified letters. The case-report forms of all patients who were lost to follow-up were reviewed to ensure that the withdrawal was not the result of an adverse event.

Patients with an SeDBP >120 mm Hg or a seated systolic BP (SeSBP) <90 mm Hg at any time during the study (including the washout phase) were removed at that time, and their original antihypertensive regimen was reinstituted or appropriate therapy initiated. The maximum allowable SeSBP was left to the discretion of the investigator. Efficacy and safety were evaluated after 2, 4, 6, and 8 weeks of blinded treatment.

A physical examination was performed at screening, and vital signs, including BP and heart rate, were obtained at all scheduled visits. A 12-lead electrocardiogram was performed at screening, randomization, and week 8, and was analyzed by eResearch Technology (Philadelphia, Pennsylvania). BP was measured using a validated automated BP-monitoring device (Model HEM-705CP, Omron Healthcare, Inc., Bannockburn, Illinois) with a cuff of an appropriate size. After the patient had rested for 5 minutes, 3 separate seated BP (SeBP) measurements were obtained at least 1 minute apart, and the mean of the 3 measurements was recorded.

Standardization across investigator sites was maintained through establishment of a detailed clinical protocol and through monitoring for adherence to the protocol by Medpace Inc., Cincinnati, Ohio.

Efficacy Variables

The primary efficacy variable was the change from baseline in mean SeDBP at week 8, using last-observation-carried-forward (LOCF) methodology for patients who did not complete the study protocol. Secondary efficacy variables included the change from baseline in mean SeSBP at week 8 (LOCF); the mean change from baseline in SeDBP and SeSBP at weeks 2, 4, 6, and 8 without LOCF; and the proportion of patients achieving the JNC 7–recommended BP goal (<140/90 mm Hg; <130/80 mm Hg for patients with diabetes[11]) at weeks 2, 4, 6, and 8 without LOCF and at week 8 with LOCF. In addition, the proportions of patients in the intention-to-treat (ITT) population (including those with diabetes) achieving BP thresholds of <120/80, <130/80, <130/85, and <140/90 mm Hg at week 8 (LOCF) was examined.

Safety Assessments and Evaluation of Edema

Safety was monitored by assessing the incidence of adverse events at each visit and by performing laboratory tests (standard serum chemistry and hematology panel, and dipstick urinalysis [with microscopy when

results were abnormal]) at the randomization visit and at week 8. Laboratory tests were conducted at a single certified central laboratory (Pharmaceutical Product Development Global Central Laboratory, Highland Heights, Kentucky), which used flow cytometry for hematology variables (Coulter SKTS or LH 750, Beckman Coulter Inc., Fullerton, California), spectrophotometry for chemistry variables (Hitachi 747 [Hitachi High Technologies America Inc., San Jose, California] or Roche Modular Analyzer [Roche Diagnostics Corp., Indianapolis, Indiana]), high-performance liquid chromatography for glycosylated hemoglobin (Tosoh 2.2 Plus, Tosoh Bioscience Inc., South San Francisco, California), and reflectance photometry for urinalysis (Atlas Urine Chemistry Analyzer, Siemens Healthcare Diagnostics Inc., Tarrytown, New York). Tests performed on different analyzers were extensively cross-validated for comparability. Investigators received the results and evaluated the clinical significance of findings that were outside the laboratory's reference ranges while still blinded to patients' treatment allocation.

An *adverse event* was defined as any untoward occurrence in study subjects from the time they signed the informed-consent form until 14 days after the last intake of study medication. All adverse events, whether detected by the investigator or reported by the patient, were recorded on the case-report form, with the date of occurrence, time of onset, duration, likely relationship to study medication, action taken, patient outcome, and whether the event met US Food and Drug Administration criteria for a serious adverse event. A *treatment-emergent adverse event* (TEAE) was defined as any event occurring after the first dose of randomized treatment or that occurred before the randomized-treatment phase but worsened after randomization. The likelihood of an adverse event being related to study medication was assessed by investigators as either *definitely related* (TEAE follows a reasonable temporal sequence from study-product administration, abates on discontinuation of the study product, and is confirmed by reappearance of the reaction on repeat exposure [rechallenge]); *probably related* (TEAE follows a reasonable temporal sequence from study-product administration, abates on discontinuation of the study product, and cannot reasonably be explained by the known characteristics of the patient's clinical state); *possibly related* (TEAE follows a reasonable temporal sequence from study-product administration and could have been produced by the patient's state or by other types of therapy administered to the patient); *unlikely to be related* (the temporal relationship between the TEAE and study-product administration is such that the drug is not likely to have had any reasonable association with the observed event and could have been produced by the patient's clinical condition or by other types of therapy administered to the patient); or *unrelated* (TEAE is definitely produced by the patient's clinical condition or by other types of therapy administered to the patient and does not follow a temporal sequence from study-product administration).

If the investigator found that the assigned study medication was not efficacious (ie, BP was not controlled or worsened during the randomized-treatment phase), she or he was required to report this as an adverse event. The terms used for this reporting could include *hypertension*, *systolic hypertension*, *diastolic hypertension*, *accelerated hypertension*, *blood pressure increased*, *diastolic blood pressure increased*, and *blood pressure inadequately controlled*. As noted earlier, patients with an SeDBP >120 mm Hg were removed from the trial.

The occurrence and severity of peripheral edema were assessed at all scheduled clinic visits. If peripheral edema (including the terms *edema*; *edema, peripheral*; *pitting edema*; *generalized edema*; and *localized edema*) was present, the investigators rated its severity on a case-report form using the following 5-point scale: 0 = no edema; 1 = mild pitting edema/slight indentation; 2 = moderate pitting edema/moderate indentation; 3 = deep pitting edema/indentation remains; and 4 = leg remains swollen. When an increase in edema category occurred after randomization, investigators were encouraged to report this as an adverse event. The methods used to evaluate peripheral edema were not validated but were consistent with those used in clinical practice.

Statistical Analysis

It was estimated that 158 patients per treatment group would be needed (total population, 1894) to detect a 3–mm Hg difference in DBP between monotherapy and combination therapy with 80% power at a 1-sided level of $P < 0.01$, assuming a common SD of 7.5 mm Hg. To achieve even distribution among treatment groups, the randomization process included stratification factors for age group (≥65 years,

<65 years) and diabetic status. Approximately 20% of randomized patients were to be aged ≥65 years.

ITT analysis was used for the efficacy evaluations and included all patients who took ≥1 dose of randomized, double-blind study medication, had a baseline BP measurement, and had ≥1 BP measurement after taking randomized, double-blind study medication. The population for the safety assessments consisted of all patients who took ≥1 dose of randomized, double-blind study medication, including both active treatment and placebo.

Baseline characteristics that were continuous variables were summarized using mean (SD), and categorical variables were summarized using frequency counts and percentages. Differences between treatment groups in baseline demographic characteristics were evaluated using an analysis-of-variance model for continuous variables and a χ^2 test for categorical variables.

Hommel's procedure[20] was used to adjust *P* values for testing the null hypotheses that there would be no difference between the 6 combination-therapy regimens and their respective monotherapy components in the change from baseline in SeDBP at week 8, LOCF (primary), and the change from baseline in SeSBP at week 8, LOCF (secondary), and to control the overall 1-sided type I error rate at 0.025. One-sided *P* values for testing the null hypotheses were obtained from an analysis-of-covariance (ANCOVA) model with fixed effects for treatment group, diabetic status (with or without diabetes), and age group (≥65 years or <65 years), and baseline BP as a covariate. The least squares mean (LSM) and corresponding SE and 2-sided 95% CI, as well as the differences in LSM, SE, and 2-sided 95% CI, were derived for continuous end-point variables from the ANCOVA model. The ANCOVA model was also used to compare each monotherapy with placebo. For categorical variables (eg, the proportion of patients achieving the BP goal at weeks 2, 4, 6, and 8), a χ^2 test was used to test for significant differences between treatment groups. Other categorical variables (proportion of patients achieving BP thresholds) were summarized using frequency counts and percentages (statistical comparisons were not performed).

The study was not powered to detect differences in the incidence of adverse events between treatment groups. However, when an apparent difference was identified in the incidence of edema between the amlodipine 10-mg monotherapy and combination-therapy groups, the incidences were compared retrospectively using the Fisher exact test. In addition, a post hoc Cochran-Armitage trend analysis[21] was undertaken to evaluate whether the differential edema rates were dose related.

RESULTS

Study Population

Of 4234 patients who entered the washout phase, 1940 were randomized and 1689 completed the study (**Figure 1**). The most common reasons for withdrawal during the randomized-treatment phase were adverse events (114 patients), including lack of efficacy (43 patients). The mean number of patients enrolled at each site was 13.

Among the 1940 randomized patients, 1054 (54.3%) were male, 1385 (71.4%) were white, and 481 (24.8%) were black. The mean age of randomized patients was 54.0 years, and the mean baseline SeBP was 164/102 mm Hg. At baseline, 1538 patients (79.3%) had stage 2 hypertension (SBP ≥160 mm Hg or DBP ≥100 mm Hg). Three hundred eighty-four patients (19.8%) were aged ≥65 years, 261 (13.5%) had diabetes, 1254 (64.6%) were overweight or obese (body mass index ≥30 kg/m^2), and 1274 (65.7%) had been receiving antihypertensive therapy. There were no statistically significant differences in demographic or other baseline characteristics between treatment groups (**Table I**).

At baseline, 264 of the 1940 randomized patients (13.6%) had peripheral edema. Edema was graded as mild in 215 patients (11.1%), moderate in 38 (2.0%), and deep pitting edema with minor leg swelling in 11 (0.6%). No patient had deep pitting edema with major leg swelling at baseline.

Efficacy

All active treatments and placebo were associated with significant reductions in SeDBP from baseline ($P < 0.001$), with the greatest reductions occurring in the groups that received combination therapy (**Figure 2**). Combination therapy was associated with dose-related changes in mean (SD) SeDBP at week 8 that ranged from –13.8 (7.48) mm Hg with OM/AML 10/5 mg to –19.0 (8.90) mm Hg with OM/AML 40/10 mg. For monotherapy, the changes in SeDBP were –8.3 (9.28), –9.2 (9.73), and –10.2 (10.69) mm Hg with OM 10, 20, and 40 mg, respectively; –9.4 (8.25) and –12.7 (8.25) mm Hg with AML 5 and 10 mg, respectively;

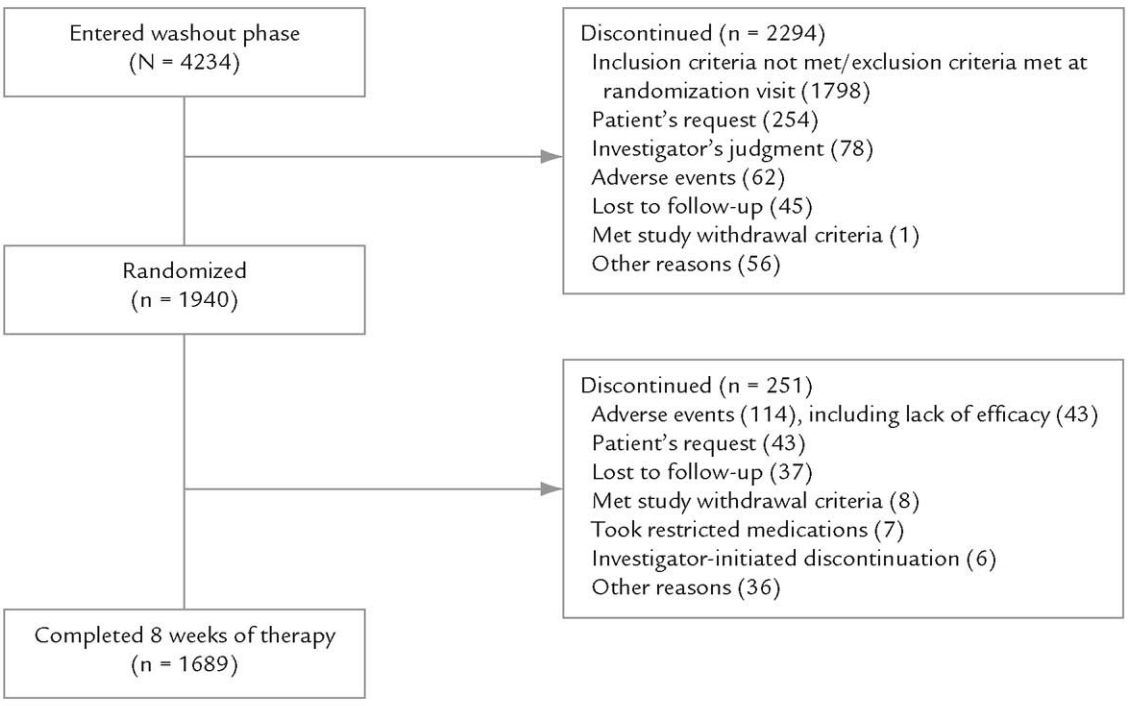

Figure 1. Patient disposition.

and −3.1 (10.67) mm Hg for placebo (**Table II**). All SeDBP reductions in the combination-therapy groups were significantly greater than those in the corresponding monotherapy groups ($P < 0.001$) (**Table II**).

The changes in mean SeSBP at week 8 followed a similar pattern to the changes in mean SeDBP, with significant reductions from baseline in all active-treatment groups ($P < 0.001$) and the placebo group ($P = 0.024$). The combinations were associated with dose-dependent mean (SD) changes ranging from −24.2 (13.96) mm Hg with OM/AML 10/5 mg to −30.1 (15.91) mm Hg with OM/AML 40/10 mg (**Table II**). For monotherapy, the mean changes in SeSBP were −11.5 (15.23), −13.8 (15.90), and −16.1 (16.58) mm Hg with OM 10, 20, and 40 mg, respectively; −14.9 (14.95) and −19.7 (16.52) mm Hg with AML 5 mg and 10 mg, respectively; and −4.8 (18.70) mm Hg with placebo. The mean reductions in SeSBP were significantly greater for all combination-therapy groups than for the component monotherapy groups ($P < 0.001$). The LSM (SE) changes in SeSBP are summarized in **Table II**. In all active-treatment groups, the greatest mean reduction in SeBP occurred between baseline and week 2. The reductions in SeDBP and SeSBP plateaued by week 4 and were maintained across all treatment groups, but with no further marked reductions.

The BP goal (<140/90 mm Hg; <130/80 mm Hg for patients with diabetes) was achieved by week 8 (LOCF) in 20.0% to 36.3% of patients receiving OM monotherapy (10 and 40 mg, respectively) and 21.1% to 32.5% of patients receiving AML monotherapy (5 and 10 mg, respectively), compared with 8.8% of patients in the placebo group (**Table III**). Rates of goal achievement at week 8 (LOCF) were greatest in the combination-therapy arms, ranging from 35.0% with OM/AML 10/5 mg to 53.2% with OM/AML 20/10 mg. Differences in rates of achievement of the BP goal between treatment groups were statistically significant at all time points ($P < 0.001$) and were consistently higher with combination therapy than with the component monotherapies ($P < 0.005$) (**Table III**).

The proportions of patients achieving the predefined BP thresholds at week 8 (LOCF) reflected a similar pattern; overall, the proportion of patients achieving each threshold was highest in the groups

Table I. Demographic and other baseline characteristics. There were no significant differences between groups.

	Olmesartan			Amlodipine		Olmesartan/Amlodipine						
Variable	10 mg (n = 161)	20 mg (n = 161)	40 mg (n = 162)	5 mg (n = 161)	10 mg (n = 163)	10/5 mg (n = 163)	20/5 mg (n = 161)	40/5 mg (n = 162)	10/10 mg (n = 162)	20/10 mg (n = 160)	40/10 mg (n = 162)	Placebo (n = 162)
Age, mean (SD), y	53.8 (11.0)	53.6 (10.8)	53.9 (10.6)	53.4 (11.4)	54.1 (10.6)	53.7 (11.8)	54.3 (10.9)	53.7 (11.3)	54.3 (10.5)	54.3 (11.6)	54.1 (12.2)	54.7 (10.9)
Sex, no. (%)												
Male	87 (54.0)	90 (55.9)	82 (50.6)	87 (54.0)	98 (60.1)	84 (51.5)	83 (51.6)	97 (59.9)	94 (58.0)	71 (44.4)	88 (54.3)	93 (57.4)
Female	74 (46.0)	71 (44.1)	80 (49.4)	74 (46.0)	65 (39.9)	79 (48.5)	78 (48.4)	65 (40.1)	68 (42.0)	89 (55.6)	74 (45.7)	69 (42.6)
Race,* no. (%)												
White	119 (73.9)	118 (73.3)	111 (68.5)	113 (70.2)	120 (73.6)	121 (74.2)	111 (68.9)	115 (71.0)	113 (69.8)	107 (66.9)	123 (75.9)	114 (70.4)
Black	32 (19.9)	36 (22.4)	44 (27.2)	42 (26.1)	39 (23.9)	34 (20.9)	43 (26.7)	40 (24.7)	44 (27.2)	47 (29.4)	35 (21.6)	45 (27.8)
Other†	10 (6.2)	8 (5.0)	7 (4.3)	7 (4.3)	5 (3.1)	10 (6.1)	9 (5.6)	7 (4.3)	6 (3.7)	6 (3.8)	6 (3.7)	3 (1.9)
Ethnicity, no. %												
Hispanic	23 (14.3)	23 (14.3)	23 (14.2)	20 (12.4)	20 (12.3)	21 (12.9)	21 (13.0)	20 (12.3)	16 (9.9)	25 (15.6)	20 (12.3)	13 (8.0)
Weight, kg												
Mean (SD)	95.5 (22.3)	95.4 (22.0)	94.3 (21.9)	95.8 (21.5)	96.2 (21.5)	94.3 (21.0)	95.6 (21.1)	93.4 (20.1)	95.9 (22.8)	94.1 (22.4)	94.6 (24.1)	96.3 (22.6)
Range	52–173	45–175	43–188	45–172	48–172	45–151	51–171	54–174	55–185	57–147	46–172	52–181
Body mass index, mean (SD), kg/m^2	33.5 (6.8)	32.9 (6.8)	33.6 (6.9)	34.1 (7.8)	33.3 (7.4)	33.3 (6.5)	34.0 (7.2)	32.5 (6.4)	33.2 (7.0)	33.9 (7.2)	33.2 (7.3)	33.9 (7.6)
Diabetes, no. (%)	20 (12.4)	22 (13.7)	22 (13.6)	22 (13.7)	23 (14.1)	23 (14.1)	22 (13.7)	18 (11.1)	20 (12.3)	22 (13.8)	24 (14.8)	23 (14.2)

(continued)

Table I. (Continued)

Variable	Olmesartan			Amlodipine		Olmesartan/Amlodipine						Placebo (n = 162)
	10 mg (n = 161)	20 mg (n = 161)	40 mg (n = 162)	5 mg (n = 161)	10 mg (n = 163)	10/5 mg (n = 163)	20/5 mg (n = 161)	40/5 mg (n = 162)	10/10 mg (n = 162)	20/10 mg (n = 160)	40/10 mg (n = 162)	
Previously treated for hypertension, no. (%)	101 (62.7)	108 (67.1)	109 (67.3)	106 (65.8)	102 (62.6)	115 (70.6)	102 (63.4)	100 (61.7)	108 (66.7)	104 (65.0)	109 (67.3)	110 (67.9)
Seated blood pressure, mean (SD), mm Hg												
SeSBP	162.9 (16.7)	164.1 (16.5)	162.8 (15.7)	162.6 (17.2)	163.5 (15.9)	165.5 (15.6)	163.8 (14.9)	161.7 (14.8)	162.5 (15.6)	164.1 (14.9)	165.7 (16.7)	166.5) (17.6)
SeDBP	101.8 (5.9)	101.5 (4.6)	101.2 (5.1)	101.5 (5.2)	101.6 (4.8)	102.1 (5.4)	101.7 (5.1)	100.9 (4.8)	101.4 (5.5)	101.2 (4.7)	102.4 (5.8)	102.3 (4.8)
Edema present, no. (%)	19 (11.8)	20 (12.4)	32 (19.8)	18 (11.2)	22 (13.5)	20 (12.3)	29 (18.0)	17 (10.5)	24 (14.8)	18 (11.3)	25 (15.4)	20 (12.3)

SeSBP = seated systolic blood pressure; SeDBP = seated diastolic blood pressure.

*Race and ethnicity were separate questions. Patients could choose >1 race, so total of numbers may exceed 100%.

†*Other* included Asian (n = 36), Native American/Alaskan (n = 11), Native Hawaiian/Pacific Islander (n = 1), and other race not defined (n = 36).

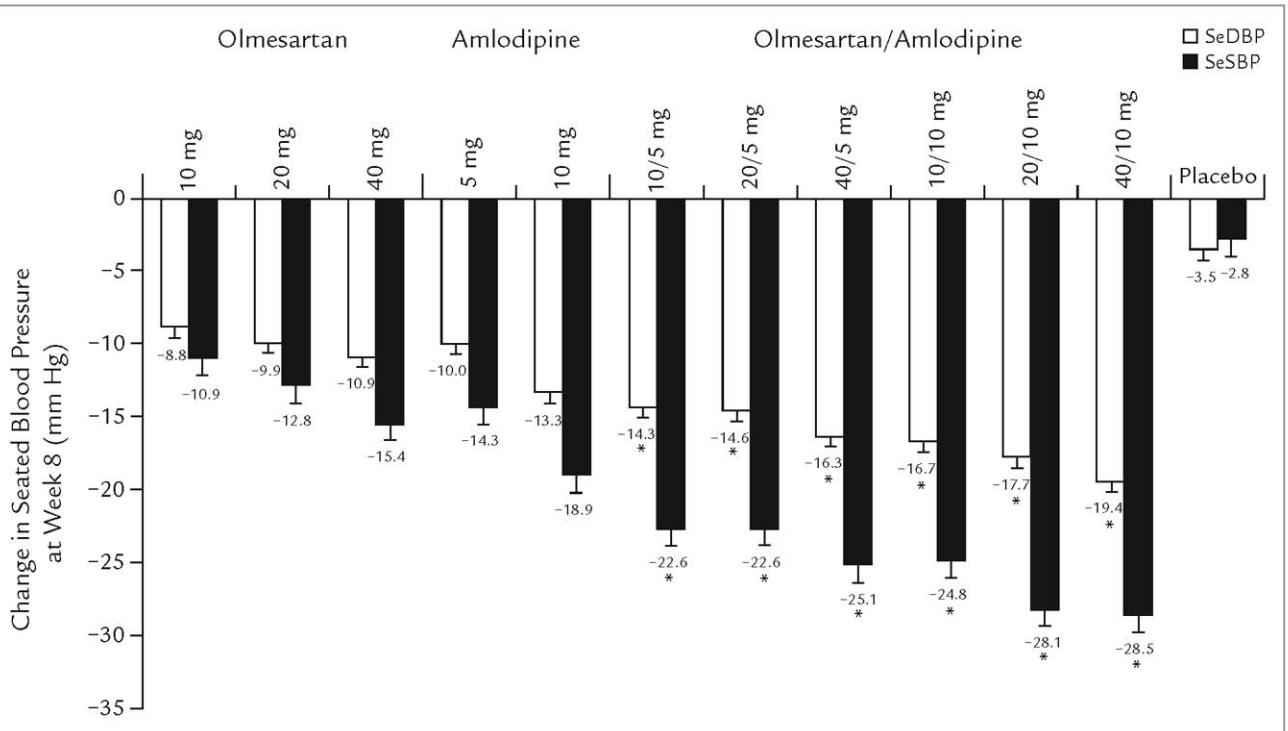

Figure 2. Least squares mean (SE) reduction from baseline in seated diastolic blood pressure (SeDBP) and seated systolic blood pressure (SeSBP) after 8 weeks of treatment with olmesartan medoxomil or amlodipine, alone and in combination (last observation carried forward). *P < 0.001 versus monotherapy with either component at the same dosage.

receiving OM/AML 20/10 mg or 40/10 mg (**Figure 3**). The proportions of all patients (including those with diabetes) achieving the BP threshold of <140/90 mm Hg with the highest doses of monotherapy and combination therapy were 38.1% for OM 40 mg, 35.0% for AML 10 mg, and 54.0% for OM/AML 40/10 mg, compared with 10.0% for placebo. Similarly, the proportions of patients achieving the BP threshold of <130/80 mm Hg were 13.8% for OM 40 mg, 7.4% for AML 10 mg, 23.0% for OM/AML 40/10 mg, and 2.5% for placebo. In addition, 77.6% of patients receiving OM/AML 40/10 mg achieved an SeDBP <90 mm Hg, compared with 18.1% of those receiving placebo.

Safety and Tolerability

One thousand twenty patients (52.6%) experienced an adverse event during treatment, with an overall incidence of 45.3% to 58.9% across active-treatment groups and 56.2% for placebo (**Table IV**). Approximately half of these adverse events were considered by the investigator to be definitely, probably, or possibly related to study medication. Five hundred twenty-one patients (26.9%) experienced a drug-related TEAE, with an incidence of 19.6% to 33.1% across active-treatment groups and 29.6% for placebo. There were no apparent differences in the overall incidence of TEAEs across treatment groups, and the majority of adverse events were considered mild in severity.

Edema was the most common TEAE, occurring in 385 of 1940 patients (19.8%) (**Table IV**). The frequency of edema was greatest among patients receiving AML 10-mg monotherapy (60/163 [36.8%]). The frequency of edema was lower in the groups in which AML 10 mg was combined with OM 10 mg (43/162 [26.5%]), 20 mg (41/160 [25.6%]), or 40 mg (38/162 [23.5%]), reaching statistical significance relative to AML 10 mg in the groups that received OM/AML 20/10 mg (P = 0.032) and 40/10 mg (P = 0.011). The frequency of edema was lowest in the OM monotherapy groups (10 mg: 23/161 [14.3%]; 20 mg: 16/161 [9.9%]; 40 mg: 30/162 [18.5%]), the AML 5-mg monotherapy group (21/161 [13.0%]), and the pla-

Table II. Change in seated diastolic blood pressure (SeDBP) and seated systolic blood pressure (SeSBP) from baseline to week 8 in the intention-to-treat population (last observation carried forward).

Group	No. of Patients	Change in SeDBP, mm Hg		Change in SeSBP, mm Hg	
		Mean (SD)	LS Mean (SE)	Mean (SD)	LS Mean (SE)
Olmesartan					
10 mg	160	−8.3 (9.28)*	−8.8 (0.75)*	−11.5 (15.23)*	−10.9 (1.24)*
20 mg	159	−9.2 (9.73)*	−9.9 (0.75)*	−13.8 (15.90)*	−12.8 (1.25)*
40 mg	160	−10.2 (10.69)*	−10.9 (0.75)*	−16.1 (16.58)*	−15.4 (1.24)*
Amlodipine					
5 mg	161	−9.4 (8.25)*	−10.0 (0.75)*	−14.9 (14.95)*	−14.3 (1.24)*
10 mg	163	−12.7 (8.25)*	−13.3 (0.74)*	−19.7 (16.52)*	−18.9 (1.23)*
Olmesartan/amlodipine					
10/5 mg	163	−13.8 (7.48)*	−14.3 (0.74)*	−24.2 (13.96)*	−22.6 (1.23)*
20/5 mg	160	−14.0 (9.07)*	−14.6 (0.75)*	−23.6 (14.86)*	−22.6 (1.24)*
40/5 mg	157	−15.5 (8.15)*	−16.3 (0.76)*	−25.4 (14.70)*	−25.1 (1.26)*
10/10 mg	161	−16.0 (8.62)*	−16. 7 (0.75)*	−25.3 (14.88)*	−24.8 (1.24)*
20/10 mg	158	−17.0 (8.04)*	−17.7 (0.75)*	−29.2 (16.72)*	−28.1 (1.25)*
40/10 mg	161	−19.0 (8.90)*	−19.4 (0.74)*	−30.1 (15.91)*	−28.5 (1.24)*
Placebo	160	−3.1 (10.67)*	−3.5 (0.75)*	−4.8 (18.70)†	−2.8 (1.25)†

LS = least squares.
*$P < 0.001$.
†$P < 0.05$.

cebo group (20/162 [12.3%]). Rates of edema in the groups receiving OM 10 to 40 mg in combination with AML 5 mg ranged from 18.0% to 20.9% (OM/AML 10/5 mg: 34/163 [20.9%]; OM/AML 20/5 mg: 29/161 [18.0%]; OM/AML 40/5 mg: 30/162 [18.5%]). A retrospective Cochran-Armitage trend analysis of the AML 10-mg, OM/AML 10/10-mg, OM/AML 20/10-mg, and OM/AML 40/10-mg groups indicated a statistically significant reduction in the incidence of edema with increasingly higher doses of OM combined with AML 10 mg ($P = 0.009$). Most occurrences of edema in all treatment groups were mild to moderate in severity. Severe edema occurred in 5 of 1940 (0.3%) patients: 1 of 161 patients (0.6%) in the AML 5-mg group, 2 of 163 patients (1.2%) in the AML 10-mg group, 1 of 162 patients (0.6%) in the OM/AML 10/10-mg group, and 1 of 162 patients (0.6%) in the OM/AML 40/10-mg group.

Other common adverse events included headache (130/1940 [6.7%]), dizziness (76/1940 [3.9%]), and fatigue (62/1940 [3.2%]), with no consistent differences between active-treatment groups (**Table IV**). The incidence of headache was highest in the placebo group (23/162 [14.2%]).

Lack of efficacy, as previously defined, was reported as an adverse event in 48 patients (2.5%): 7 of 161 (4.3%) in the OM 10-mg monotherapy group, 8 of 161 (5.0%) in the OM 20-mg monotherapy group, 6 of 162 (3.7%) in the OM 40-mg monotherapy group, 4 of 161 (2.5%) in the AML 5-mg monotherapy group, 2 of 163 (1.2%) in the AML 10-mg monotherapy group, 1 of 163 (0.6%) in the OM/AML 10/5-mg group, 3 of 161 (1.9%) in the OM/AML 20/5-mg group, 2 of 162 (1.2%) in the OM/AML 40/5-mg group, 1 of 162 (0.6%) in the OM/AML 10/10-mg group, 1 of 160 (0.6%) in the OM/AML 20/10-mg group, and 13 of 162 (8.0%) in the placebo group. None of the patients receiving OM/AML 40/10 mg had uncontrolled BP during treatment.

Nine of 1940 patients (0.5%) experienced hypotension: 1 patient (0.6%) each in the OM 10-mg (n =

Table III. Patients achieving the blood pressure goal (<140/90 mm Hg for patients with uncomplicated hypertension; <130/80 mm Hg for patients with diabetes) after 8 weeks of treatment with olmesartan or amlodipine, alone and in combination (last observation carried forward).

Treatment Group	No. (%)
Olmesartan	
10 mg (n = 160)	32 (20.0)
20 mg (n = 159)	42 (26.4)
40 mg (n = 160)	58 (36.3)
Amlodipine	
5 mg (n = 161)	34 (21.1)
10 mg (n = 163)	53 (32.5)
Olmesartan/amlodipine	
10/5 mg (n = 163)	57 (35.0)*†
20/5 mg (n = 160)	68 (42.5)*‡
40/5 mg (n = 157)	80 (51.0)‡§
10/10 mg (n = 161)	79 (49.1)*†
20/10 mg (n = 158)	84 (53.2)*‡
40/10 mg (n = 161)	79 (49.1)‡§
Placebo (n = 160)	14 (8.8)

*$P < 0.001$ versus monotherapy with olmesartan at the same dosage.
†$P = 0.003$ versus monotherapy with amlodipine at the same dosage.
‡$P < 0.001$ versus monotherapy with amlodipine at the same dosage.
§$P < 0.005$ versus monotherapy with olmesartan at the same dosage.

161), AML 10-mg (n = 163), and OM/AML 40/5-mg groups (n = 162), and 2 patients (1.2%–1.3%) each in the OM/AML 10/10-mg (n = 162), 20/10-mg (n = 160), and 40/10-mg groups (n = 162). Of the 7 patients with drug-related hypotension, 1 each in the OM/AML 10/10-mg and 40/10-mg groups were removed from the study because of moderate or severe hypotension.

Serious TEAEs occurred in 25 of 1940 patients (1.3%). Only 1 of these was considered drug related (**Table IV**): a patient receiving OM 20 mg had a nonfatal cerebrovascular accident (CVA) that the investigator considered probably related to study medication, as the patient's BP was not fully controlled.

Two patients died during the study: 1 had a fatal CVA during the washout phase and the other (a placebo recipient) was a victim of homicide during the randomized-treatment phase. Neither death was considered treatment related. The patient who died during the washout phase had a BP of 155/87 mm Hg at the assessment 10 days before the CVA. Of the 1940 randomized patients, 114 (5.9%) discontinued treatment due to any adverse event (**Table IV**): 40 of 484 (8.3%) in the 3 OM-monotherapy groups, 20 of 324 (6.2%) in the 2 AML-monotherapy groups, 33 of 970 (3.4%) in the 6 combination-therapy groups, and 21 of 162 (13.0%) in the placebo group. The adverse events leading to study discontinuation were considered treatment related in 74 patients (3.8% of the total study group; 64.9% of patients discontinuing treatment because of an adverse event).

Although small mean changes were observed in serum chemistry, hematology, and urinalysis parameters, there was no consistent pattern and no apparent relationship to dose or compound. None of the mean changes were considered clinically significant. Although there were statistically significant increases from baseline in mean platelet count with AML 5-mg monotherapy ($P = 0.002$) and 10-mg monotherapy ($P < 0.001$) and all doses of the combination ($P < 0.001$), the magnitude of the increase was <10% in all groups and was not considered clinically meaningful (the highest increase was $22.08 \times 10^3/mm^3$ with AML 10 mg). A small number of patients developed laboratory abnormalities outside the prespecified safety ranges (**Table V**), but only 1 patient (receiving AML 10-mg monotherapy) was removed from the study because of increases in alkaline phosphatase and γ-glutamyltransferase. No differences in serum chemistry, hematology, or urinalysis parameters between treatment groups were considered clinically relevant by the investigators.

DISCUSSION

This 8-week study found that all doses of the combination of OM and AML were significantly more effective than the component monotherapies in reducing both SeDBP and SeSBP ($P < 0.001$). In addition, the proportion of patients achieving the BP goal (<140/90 mm Hg; <130/80 mm Hg in patients with diabetes) was greatest in the combination-therapy arms, with ~50% of patients achieving BP control with the higher doses of combination therapy. In addition, 54.0% of patients receiving the highest dose of OM/AML

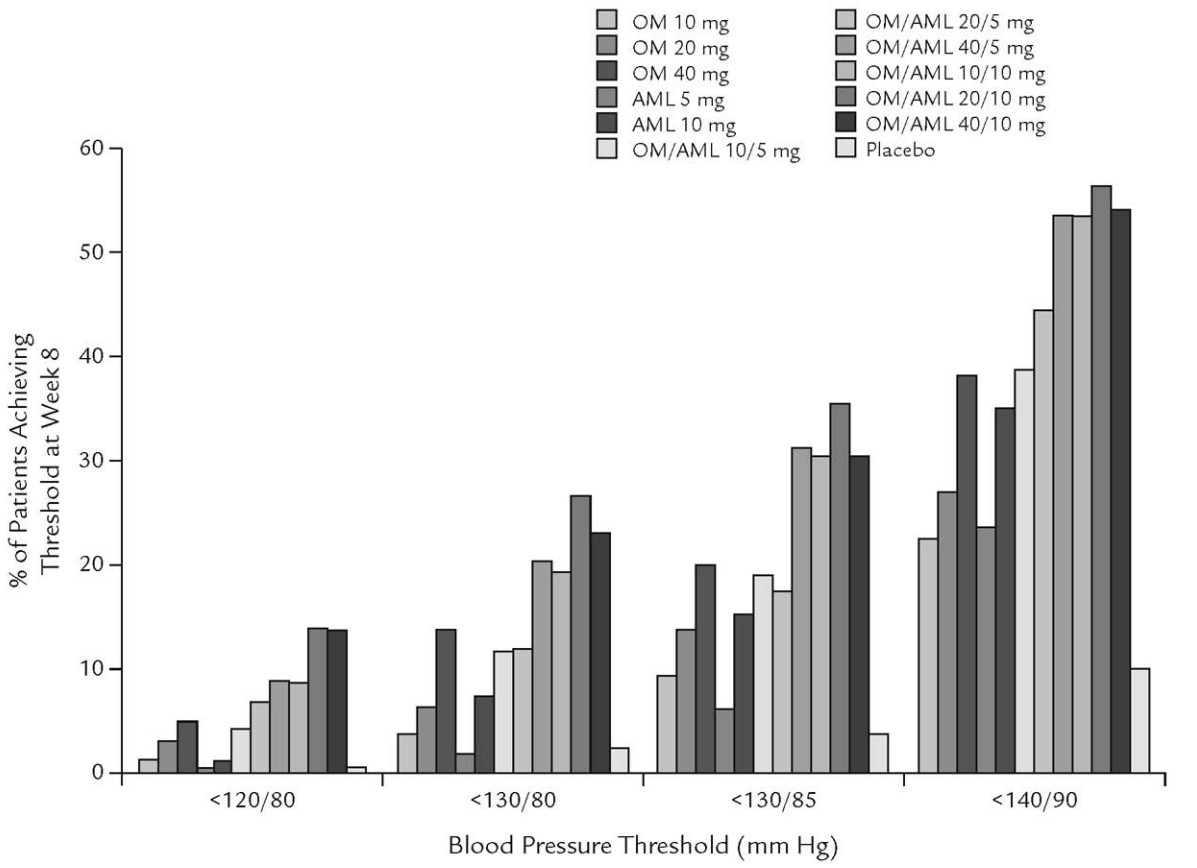

Figure 3. Proportions of patients in the intention-to-treat population achieving blood pressure thresholds at week 8 (last observation carried forward). OM = olmesartan medoxomil; AML = amlodipine; OM/AML = olmesartan/amlodipine.

achieved a BP <140/90 mm Hg at week 8. All OM and AML monotherapy and combination regimens were well tolerated, and no unexpected safety concerns were identified.

The finding of dose-dependent efficacy with the combination of OM/AML is consistent with results from similar studies of other fixed-dose combinations,[22–28] as well as from studies that specifically examined the combination of another ARB, valsartan, with AML.[29,30] As in the present trial, these studies found higher BP reductions and greater proportions of patients achieving BP targets with the combination therapy than with the component monotherapies.

A number of fixed-dose antihypertensive combinations are available in the United States, including ARBs combined with a diuretic (hydrochlorothiazide) and ACE inhibitors combined with a diuretic or CCB. The treatment approach underlying these combinations is consistent with the JNC 7 recommendation that combination agents should consist of drugs that act through different antihypertensive pathways to maximize the therapeutic benefit.[11]

OM and AML have complementary mechanisms of action, accounting for their additive antihypertensive effects. The vasodilatory action of CCBs stimulates counterregulatory mechanisms such as sympathetic activation and activation of the RAAS.[13] These mechanisms reduce the BP-lowering effects of CCBs. However, an added ARB or ACE inhibitor counteracts RAAS activation, thereby maximizing the BP-lowering effect of the CCB while having an antihypertensive effect of its own.

Both European and US guidelines for the management of hypertension have noted the importance of

Table IV. Number (%) of patients having treatment-emergent adverse events (TEAEs) occurring in ≥3% of patients in any group during 8 weeks of treatment with olmesartan or amlodipine, alone and in combination.

	Olmesartan			Amlodipine		Olmesartan/Amlodipine						
Variable	10 mg (n = 161)	20 mg (n = 161)	40 mg (n = 162)	5 mg (n = 161)	10 mg (n = 163)	10/5 mg (n = 163)	20/5 mg (n = 161)	40/5 mg (n = 162)	10/10 mg (n = 162)	20/10 mg (n = 160)	40/10 mg (n = 162)	Placebo (n = 162)
Any TEAE	88 (54.7)	83 (51.6)	78 (48.1)	73 (45.3)	96 (58.9)	74 (45.4)	90 (55.9)	83 (51.2)	92 (56.8)	85 (53.1)	87 (53.7)	91 (56.2)
Any discontinuations due to a TEAE	13 (8.1)	17 (10.6)	10 (6.2)	10 (6.2)	10 (6.1)	0	4 (2.5)	6 (3.7)	11 (6.8)	3 (1.9)	9 (5.6)	21 (13.0)
Any drug-related TEAE	43 (26.7)	36 (22.4)	40 (24.7)	32 (19.9)	54 (33.1)	32 (19.6)	44 (27.3)	46 (28.4)	51 (31.5)	48 (30.0)	47 (29.0)	48 (29.6)
Serious drug-related TEAE	0	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Discontinuations due to a drug-related TEAE	10 (6.2)	11 (6.8)	7 (4.3)	4 (2.5)	6 (3.7)	0	3 (1.9)	4 (2.5)	9 (5.6)	1 (0.6)	8 (4.9)	11 (6.8)
Specific TEAEs												
Edema*	23 (14.3)	16 (9.9)	30 (18.5)	21 (13.0)	60 (36.8)	34 (20.9)	29 (18.0)	30 (18.5)	43 (26.5)	41 (25.6)	38 (23.5)	20 (12.3)
Headache	9 (5.6)	14 (8.7)	14 (8.6)	13 (8.1)	8 (4.9)	4 (2.5)	9 (5.6)	6 (3.7)	10 (6.2)	11 (6.9)	9 (5.6)	23 (14.2)
Fatigue	7 (4.3)	3 (1.9)	3 (1.9)	5 (3.1)	3 (1.8)	3 (1.8)	5 (3.1)	8 (4.9)	2 (1.2)	14 (8.8)	3 (1.9)	6 (3.7)
Dizziness	5 (3.1)	10 (6.2)	8 (4.9)	5 (3.1)	4 (2.5)	3 (1.8)	8 (5.0)	7 (4.3)	6 (3.7)	5 (3.1)	6 (3.7)	9 (5.6)
Hypertension†	7 (4.3)	8 (5.0)	6 (3.7)	4 (2.5)	2 (1.2)	1 (0.6)	3 (1.9)	2 (1.2)	1 (0.6)	1 (0.6)	0	13 (8.0)
Nausea	2 (1.2)	3 (1.9)	2 (1.2)	2 (1.2)	2 (1.2)	1 (0.6)	5 (3.1)	3 (1.9)	2 (1.2)	2 (1.3)	5 (3.1)	5 (3.1)
Rash	0	0	1 (0.6)	1 (0.6)	5 (3.1)	2 (1.2)	1 (0.6)	3 (1.9)	1 (0.6)	2 (1.3)	1 (0.6)	2 (1.2)

*Combines the terms *edema*, *peripheral edema*, *pitting edema*, *generalized edema*, and *localized edema*. Patients were counted once for any instance of any of these terms.

†Combines the terms *hypertension*, *systolic hypertension*, *diastolic hypertension*, *accelerated hypertension*, *blood pressure increased*, *diastolic blood pressure increased*, and *blood pressure inadequately controlled*. Patients were counted once for any instance of any of these terms.

Table V. Number (%) of patients in the safety population developing laboratory abnormalities (values outside the predefined safety thresholds).

	Olmesartan			Amlodipine		Olmesartan/Amlodipine						
Parameter (Threshold)	10 mg (n = 161)	20 mg (n = 161)	40 mg (n = 162)	5 mg (n = 161)	10 mg (n = 163)	10/5 mg (n = 163)	20/5 mg (n = 161)	40/5 mg (n = 162)	10/10 mg (n = 162)	20/10 mg (n = 160)	40/10 mg (n = 162)	Placebo (n = 162)
Serum chemistry												
AST (>66 mU/mL)	1 (0.6)	2 (1.2)	0	1 (0.6)	0	0	1 (0.6)	0	1 (0.6)	1 (0.6)	1 (0.6)	0
ALT (>75 mU/mL)	2 (1.2)	1 (0.6)	0	1 (0.6)	0	1 (0.6)	1 (0.6)	0	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)
GGT (>87 mU/mL)	6 (3.7)	6 (3.7)	5 (3.1)	5 (3.1)	4 (2.5)*	6 (3.7)	13 (8.1)	5 (3.1)	9 (5.6)	2 (1.3)	4 (2.5)	6 (3.7)
Alkaline phosphatase (>216 mU/mL)	0	0	0	0	1 (0.6)*	0	0	0	0	0	0	1 (0.6)
Total bilirubin (>1.65 mg/dL)	0	0	0	0	1 (0.6)	0	1 (0.6)	0	0	0	1 (0.6)	1 (0.6)
Potassium (>5.0 mEq/L)	11 (6.8)	6 (3.7)	9 (5.6)	3 (1.9)	4 (2.5)	3 (1.8)	8 (5.0)	17 (10.5)	8 (4.9)	9 (5.6)	9 (5.6)	6 (3.7)
Hematology												
Hematocrit (<30%)	0	0	1 (0.6)	0	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Platelet count ($<100 \times 10^3/mm^3$)	0	0	0	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)	0	0	0	0	0

AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = γ-glutamyltransferase.
*One patient receiving this dosage developed an increase in both alkaline phosphatase and GGT and was withdrawn from the study.

combination therapy in accelerating progress toward BP goals.[11,12] In addition, these guidelines advocate use of combination therapy, when indicated, as initial treatment for patients who require reductions of >20/10 mm Hg to achieve the BP goal. However, the combination of OM and AML is not approved for the initial treatment for hypertension.

In addition to having improved BP-lowering efficacy, fixed-dose combinations may offer patient convenience compared with 2 agents taken separately. A recent meta-analysis reported that patient compliance was significantly better with fixed-dose antihypertensive combinations than with the same 2 agents administered concomitantly ($P < 0.001$).[31]

The combination of OM and AML was well tolerated in this study. The incidence of TEAEs, serious adverse events, and discontinuations due to adverse events was comparable among treatment groups, and the frequency of TEAE-related discontinuations was lower in the combination-treatment groups than in the placebo group. Edema was the only adverse event that showed a meaningful dose–response relationship. Most occurrences of edema were mild in severity, with moderate or severe edema most commonly seen in the groups receiving AML 10 mg, alone or in combination with OM. Although the incidence of edema was high in the group that received AML 10-mg monotherapy, both the incidence and severity of edema were reduced when AML 10 mg was combined with increasing doses of OM. In fact, the placebo-subtracted incidence of treatment-emergent edema was reduced by 54% when OM 40 mg was added to AML 10 mg. As expected, AML 5-mg monotherapy was associated with a lower incidence of edema than AML 10-mg monotherapy.

The reduction in edema when the higher dose of AML was combined with increasing doses of OM in this study is consistent with other reports indicating that the use of a RAAS blocker in combination with AML reduced the likelihood of AML-induced edema.[29,32,33] The present study is one of the few trials of an antihypertensive combination to actively seek out occurrences of edema and grade its severity. As a result, the incidence of edema reported here is higher than in other trials that have relied on passive reporting. For example, a factorial study of valsartan and AML that used a passive-reporting system (adverse events were volunteered by patients, elicited by general questioning, or detected on physical examination) reported edema rates of 8.7% with AML monotherapy and 3.0% with placebo,[29] compared with 13.0% to 36.8% with AML monotherapy and 12.3% with placebo in the present study. However, our findings are consistent with the incidence of edema in trials that used active edema surveillance, including studies of AML monotherapy. For example, Leonetti et al[34] reported a 19% rate of edema with AML 5 or 10 mg when symptoms were actively elicited using a patient questionnaire. Furthermore, in the Comparison of Candesartan and Amlodipine for Safety, Tolerability and Efficacy (CASTLE),[35] which used a proactive monitoring system, 22.1% of patients receiving AML 5 or 10 mg were reported to have edema. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE),[36] which also used a proactive monitoring system, 32.9% of patients receiving AML 5 or 10 mg with or without hydrochlorothiazide developed edema. The incidence of edema with the ARBs used in the foregoing studies was 8.9% for candesartan and 14.9% for valsartan, comparable to the incidence with OM in the present study (9.9%–18.5%).

The factorial design of this study provides important dose–response information about the BP-lowering effects of the combination of OM and AML. However, the study was of short duration (8 weeks) and thus had limited ability to predict long-term effectiveness or tolerability. Finally, the results of this study are applicable to the population studied (adults with mild to severe hypertension) and may not be generalizable to other populations with different characteristics.

CONCLUSIONS

In this population of adult patients with mild to severe hypertension, the OM/AML combinations were significantly better than their monotherapy components and placebo in lowering BP and achieving JNC 7 BP goals. Combination therapy was well tolerated and was associated with a lower incidence of edema relative to monotherapy with high-dose AML (10 mg).

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