ORIGINAL RESEARCH

# The TRINITY Study: distribution of systolic blood pressure reductions

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**Background:** Elevated systolic blood pressure is more difficult to control than elevated diastolic blood pressure. The objective of this prespecified analysis of the Triple Therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in Hypertensive Patients Study (TRINITY) was to compare the efficacy of olmesartan medoxomil (OM) 40 mg, amlodipine besylate (AML) 10 mg, and hydrochlorothiazide (HCTZ) 25 mg triple-combination treatment with the component dual-combination treatments in reducing elevated seated systolic blood pressure (SeSBP).

**Methods:** The 12-week TRINITY study randomized participants to either one of the three component dual-combination treatments (OM 40 mg/AML 10 mg, OM 40 mg/HCTZ 25 mg, or AML 10 mg/HCTZ 25 mg) or the triple-combination treatment. The primary outcome of this analysis was the categorical distribution of SeSBP reductions at week 12 from baseline with OM 40 mg/AML 10 mg/HCTZ 25 mg versus the dual-combination treatments.

**Results:** SeSBP reductions >50 mmHg were seen in 24.4% of participants receiving triple-combination treatment versus 8.1%–15.8% receiving dual-combination treatment. More participants receiving triple-combination treatment achieved the SeSBP target of <140 mmHg (73.6% versus 51.3%–58.8%; $P < 0.001$) and the seated blood pressure target of <140/90 mmHg (69.9% versus 41.1%–53.4%; $P < 0.001$). Prevalence and severity of adverse events were similar in all treatment groups.

**Conclusion:** Treatment with OM 40 mg/AML 10 mg/HCTZ 25 mg was well tolerated and more effective in reducing SeSBP than the dual-combination treatments.

**Keywords:** olmesartan, angiotensin receptors, calcium channel blockers, thiazide diuretics, hypertension, TRINITY

## Introduction

Approximately 33% of adults in the US (representing 78 million adults) have hypertension, one of the most prevalent risk factors for development of cardiovascular disease.[1] The risks of ischemic heart disease, heart failure, stroke, and kidney disease have all been shown to correlate directly with elevated blood pressure (BP).[2]

Historically, assessments of cardiovascular risk have focused on elevated diastolic BP (DBP);[3] however, DBP tends to level off or decrease after age 50 years, whereas systolic BP (SBP) continues to rise throughout life.[2] In a recent analysis of data from the National Health and Nutrition Examination Survey, mean SBP increased with advancing age from 115 mmHg (ages 18–39 years) to 123 mmHg (ages 40–59 years) to 136 mmHg (age ≥60 years).[4] In contrast, mean DBP rose from 69 mmHg to 75 mmHg as age increased from 18–39 years to 40–59 years, but then decreased to 68 mmHg as age further increased to ≥60 years.[4] Thus, systolic hypertension increases in prevalence

with age, becoming the most common form of hypertension after age 50 years.[2,5]

Systolic hypertension is a major risk factor for the development of cardiovascular disease, and data show that it is a more potent and accurate predictor of cardiovascular morbidity and mortality than diastolic hypertension in individuals ≥50 years of age.[2,3,6,7] In a meta-analysis of data from 61 trials, SBP was found to have approximately 20% greater predictive power for ischemic heart disease mortality than DBP.[6] Furthermore, clinical trials demonstrate that reducing SBP improves cardiovascular outcomes.[2] Another meta-analysis of data from ten trials found that improvements in cardiovascular event rates were related to reductions in SBP but not to reductions in DBP.[8]

Despite these data, systolic hypertension is frequently less well controlled than diastolic hypertension.[2,9] After 3 years of therapy in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), only 64% of patients had their SBP adequately controlled compared with 90% who had their DBP adequately controlled.[9] This inadequate management of systolic hypertension is a major contributing factor to the low rate of overall BP control.[2] It is estimated that 80% of individuals with hypertension in the US will be >50 years of age and have predominantly SBP elevations by 2020.[10] With the aging of the US population, reducing cardiovascular morbidity and mortality will require greater emphasis on successfully managing systolic hypertension.[2]

The primary study results for the Triple Therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in Hypertensive Patients Study (TRINITY; ClinicalTrials.gov identifier: NCT00649389) have been published previously.[11] The triple-drug combination of olmesartan medoxomil (OM) 40 mg, amlodipine besylate (AML) 10 mg, and hydrochlorothiazide (HCTZ) 25 mg reduced both seated DBP (primary efficacy registration requirement for OM/AML/HCTZ) and seated SBP (SeSBP) to a greater extent and enabled a larger proportion of study participants to reach BP goal than all three component dual-combination treatments.[11] We report here the unique results of a prespecified TRINITY analysis that evaluated categorical mean reductions in SeSBP with OM 40/AML 10/HCTZ 25 mg compared with each of the component dual-combination treatments.

## Methods
### Study population
The detailed study design and principal efficacy and safety results have been reported previously in the primary

TRINITY publication.[11] Briefly, TRINITY was a 12-week, prospective, randomized, double-blind, parallel-group evaluation conducted on an outpatient basis at 317 clinical sites in the US and Puerto Rico. Individuals ≥18 years of age with a mean SeBP ≥ 140/100 mmHg or ≥160/90 mmHg (off antihypertensive medication) were eligible for randomization provided they did not have a recent (≤6 months) history of myocardial infarction, coronary revascularization, or unstable angina; New York Heart Association class 3 or 4 congestive heart failure; severe renal insufficiency (defined as creatinine clearance <30 mL/minute); or uncontrolled diabetes (defined as hemoglobin A1c levels >9%). Individuals with type 1 or type 2 diabetes mellitus that was controlled by diet, insulin, or oral hypoglycemic agents on a stable dose for ≥30 days were eligible for participation. The study was conducted in accordance with the Declaration of Helsinki; the study protocol and consent forms were approved by the appropriate institutional review boards; and all individuals provided written informed consent before participation in any study procedures.

### Study design
The study included a 3-week washout period for participants already taking antihypertensive medications, followed by a 12-week double-blind treatment period (Figure 1).[11] Eligible participants were randomized (stratified by age, race, and diabetes status) at the start of the study to a treatment sequence that led to their final treatment assignment: either one of the three component dual-combination treatments or the triple-combination treatment (OM 40 mg/AML 10 mg/HCTZ 25 mg [given as the OM 40 mg/HCTZ 25 mg fixed-dose combination plus AML 10 mg given separately], OM 40 mg/AML 10 mg [fixed-dose combination], OM 40 mg/HCTZ 25 mg [fixed-dose combination], or AML 10 mg/HCTZ 25 mg [given separately]). All participants received dual-combination treatment for 2 weeks, except for a subset of 36 study participants who had not been taking antihypertensive medications for at least 3 weeks who received placebo for 2 weeks (to assess the study for nontreatment-associated BP effects, some patients received placebo for 2 weeks). All participants assigned to dual-combination treatment remained on their assigned treatment until week 4. All participants taking placebo at week 2 were switched to one of the three dual-combination treatments from week 2 to week 4. At week 4, participants were either maintained on dual-combination treatment to week 12 or switched to triple-combination treatment with OM 40 mg/AML 10 mg/HCTZ 25 mg until week 12. Participants were instructed to take
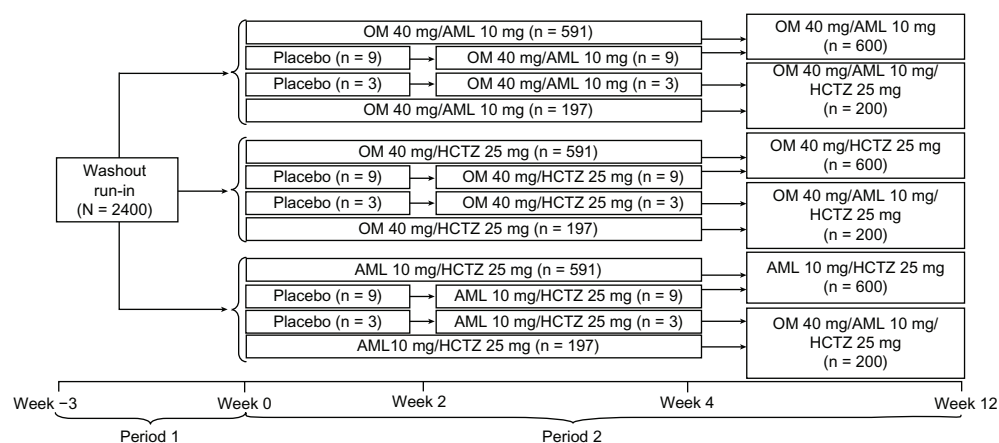
**Figure 1** Study design.
**Note:** Modified with permission from Oparil et al.[11] Copyright Elsevier (2010).
**Abbreviations:** N, total sample size; n, number; OM, olmesartan medoxomil; AML, amlodipine besylate; HCTZ, hydrochlorothiazide.

all medications at the same time (±2 hours) each day, and participants and investigators remained blinded as to which drugs were being administered at any given time during the double-blind treatment period.

## Efficacy assessments

The primary assessment for the present analysis was the distribution (or range) of SeSBP reductions at week 12 from baseline with triple-combination treatment compared with the component dual-combination treatments. For this assessment, reductions in SeSBP were categorized as >50, >40 to ≤50, >30 to ≤40, >20 to ≤30, >10 to ≤20, and ≤10 mmHg. Additional assessments (post hoc analyses) included the least squares mean reduction in SeSBP, the proportion of participants achieving the SeSBP target of <140 mmHg, and the proportion of participants achieving the SeBP target of <140/90 mmHg by treatment within each SeSBP reduction category.

## Safety assessments

Safety was assessed at all visits. Safety parameters evaluated included adverse events, physical examinations, twelve-lead electrocardiograms, and clinical laboratory tests. For this analysis, safety parameters were categorized based on randomized treatment assignment and degree of SeSBP reduction (≤40 or >40 mmHg).

## Statistical analysis

Efficacy was assessed in all study participants who had a baseline assessment of SeBP, received at least one dose of study medication, and had at least one postdose assessment of SeBP. To account for potential early termination during the double-blind treatment period, efficacy analyses were conducted by a last observation carried forward approach. Safety was assessed in all participants who received at least one dose of study medication at or beyond the week 4 visit (ie, the first time at which participants could receive triple-combination treatment). Both efficacy and safety were categorized on the basis of the degree of SeSBP reduction at week 12.

Changes in SeBP at week 12 were evaluated with an analysis of covariance model with baseline SeBP as a covariate and final randomized treatment, subgroup, and final randomized treatment by subgroup interaction as fixed effects. Least squares mean differences and standard errors, derived from this model, were used to calculate baseline changes in SeBP; 2-sided $P$-values were used to test the significance of these changes for study participants receiving triple-combination treatment versus each dual-combination treatment.

The proportion of study participants achieving SeSBP reductions of >50 mmHg, >40 mmHg to ≤50 mmHg, >30 mmHg to ≤40 mmHg, >20 mmHg to ≤30 mmHg, >10 mmHg to ≤20 mmHg, and ≤10 mmHg and the proportion of study participants reaching SeSBP (<140 mmHg) and SeBP (<140/90 mmHg) targets within these reduction categories were summarized by randomized treatment assignment using descriptive statistics. Overall treatment effects were assessed with the $\chi^2$ test, and between-treatment effects were assessed with Fisher's exact test.

## Results
### Study population
Of the 6724 individuals who were screened, 2492 were randomized and entered the double-blind treatment period,

and 2116 completed the trial.[11] The safety population included 2302 participants. The demographic and clinical characteristics at baseline by treatment assignment were similar for randomized study participants (data published in the primary TRINITY paper).[11] Overall, 52.9% of participants were male, 66.8% were white, 30.4% were black, 9.1% had chronic cardiovascular disease, 15.5% had diabetes, and 4.1% had chronic kidney disease. Mean age (standard deviation [SD]) was 55.1 (10.9) years (18.9% ≥65 years), and mean body mass index (SD) was 33.1 (7.1) kg/m² (62.4% ≥30 kg/m²). The mean (SD) duration of hypertension was 9.9 (9.6) years, and mean baseline SeBP was 168.5/100.9 mmHg.[11]

## Efficacy

Triple-combination treatment resulted in greater SeSBP reductions than the dual-combination treatments (Figure 2). SeSBP reductions of >50 mmHg were seen in 24.4% of participants receiving OM 40 mg/AML 10 mg/HCTZ 25 mg, but in only 8.1%, 9.5%, and 15.8% of participants receiving AML 10 mg/HCTZ 25 mg, OM 40 mg/AML 10 mg, and OM 40 mg/HCTZ 25 mg, respectively. SeSBP reductions of >40 mmHg to ≤50 mmHg were seen in 23.0% of participants receiving triple-combination treatment compared with 14.2%–17.6% of participants receiving dual-combination treatments. SeSBP reductions of ≤20 mmHg were seen in only 12.9% of participants receiving triple-combination treatment compared with 21.8%–28.3% of participants receiving dual-combination treatments. As a result, the overall least

squares mean reduction in SeSBP was significantly greater (−37.1 mmHg versus −27.5 mmHg to −30.0 mmHg, respectively; $P < 0.0001$),[11] and the overall mean SeBP was significantly lower (129.8/79.4 mmHg versus 137.0/83.2 mmHg and 140.0/86.4 mmHg, respectively; $P < 0.0001$) at week 12 in participants receiving triple-combination treatment than in those receiving dual-combination treatment.

For a given categorical SeSBP reduction, the baseline and week 12 SeSBP levels were similar across treatment groups (Figure 3). In general, the degree of SeSBP reduction correlated with baseline pressure (ie, the higher the SeSBP at baseline, the greater the reduction at week 12). The study participants who had the highest mean SeSBP levels at baseline (176–188 mmHg, depending on treatment) experienced the greatest therapeutic effect (lowest mean SeSBP levels) at week 12 (116–129 mmHg, depending on treatment).

Overall, triple-combination treatment was significantly more effective than the dual-combination treatments in achieving the SeSBP target of <140 mmHg (73.6% versus 51.3%–58.8%, respectively) and the SeBP target of <140/90 mmHg (69.9% versus 41.1%–53.4%, respectively) at week 12 ($P < 0.001$ for all triple- versus dual-combination comparisons).[11] The higher the categorical SeSBP reduction, the more the observed differentiation based on treatment potency, and as a result, more participants with higher baseline BP had greater achievement of
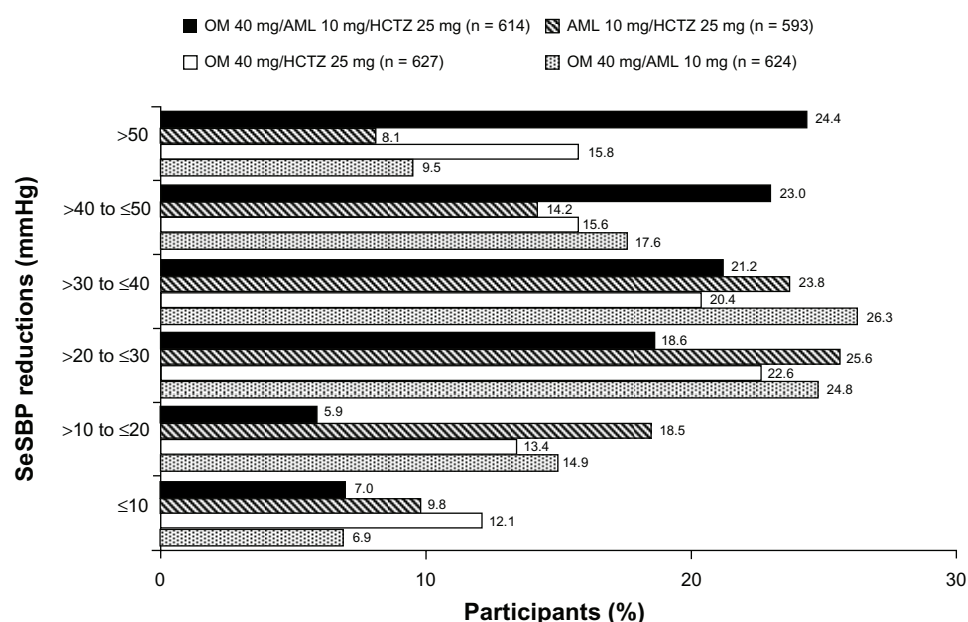


**Figure 2** Frequency distribution in SeSBP at week 12 from baseline (last observation carried forward) by treatment.
**Abbreviations:** SeSBP, seated systolic blood pressure; OM, olmesartan medoxomil; AML, amlodipine besylate; HCTZ, hydrochlorothiazide; n, number.
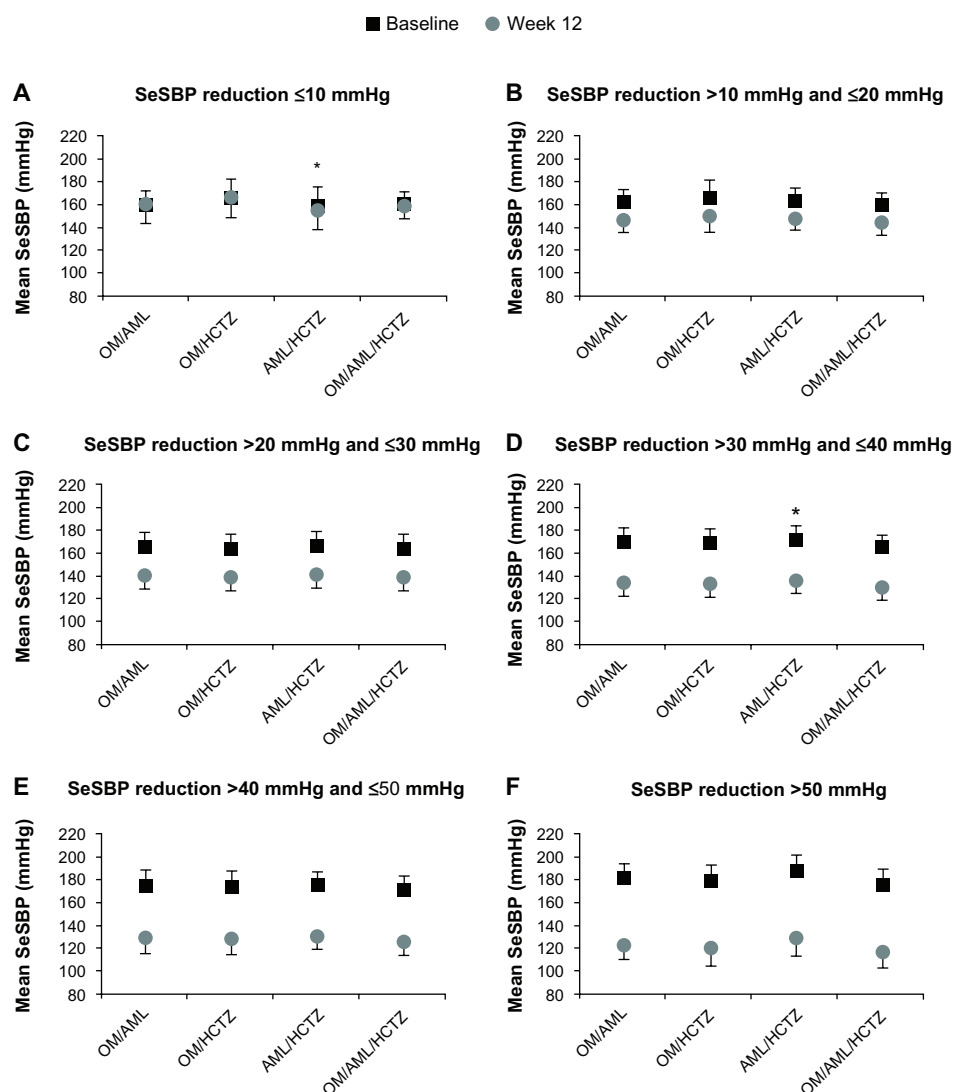
■ Baseline    ● Week 12



**Figure 3** Mean baseline and week 12 SeSBP (last observation carried forward) by treatment.
**Notes:** Mean baseline and week 12 SeSBP (last observation carried forward) by treatment among participants with a (**A**) ≤10 mmHg; (**B**) >10 mmHg and ≤20 mmHg; (**C**) >20 mmHg and ≤30 mmHg; (**D**) >30 mmHg and ≤40 mmHg; (**E**) >40 mmHg and ≤50 mmHg; and (**F**) >50 mmHg SeSBP reduction from baseline. Please see Figure 2 for the number of participants in each category. Error bars depict the standard deviation. *P < 0.05 for the least squares mean reduction in SeSBP, OM/AML/HCTZ versus dual-combination treatment.
**Abbreviations:** SeSBP, seated systolic blood pressure; OM, olmesartan medoxomil (40 mg); AML, amlodipine besylate (10 mg); HCTZ, hydrochlorothiazide (25 mg).

BP targets (Figures 4 and 5), particularly with SeSBP reductions >30 mmHg.

## Safety

No new safety concerns were identified with the triple- or dual-combination treatments that were not known to occur with the individual-component treatments. In total, 1287/2302 study participants (55.9%) had a treatment-emergent adverse event (TEAE), and 585 participants (25.4%) had a drug-related TEAE.[11] Most TEAEs were mild or moderate in severity. The prevalence and severity of adverse events did not appear to be related to either treatment or the degree of categorical SeSBP reduction (Table 1).

TEAEs with triple-combination treatment OM 40 mg/AML 10 mg/HCTZ 25 mg occurred in 56.3% and 60.5% of participants with SeSBP reductions of ≤40 mmHg and >40 mmHg, respectively. Drug-related TEAEs occurred in 26.4% and 30.1% of participants with SeSBP reductions of ≤40 mmHg and >40 mmHg, respectively. For the total study population, 2.3% of participants discontinued study participation because of a TEAE, and 1.4% of participants discontinued study participation because of a drug-related TEAE.[11] Discontinuations related to adverse events were more prevalent in participants receiving triple-combination treatment, particularly in participants with a ≤40 mmHg reduction in SeSBP across treatment groups (Table 1).
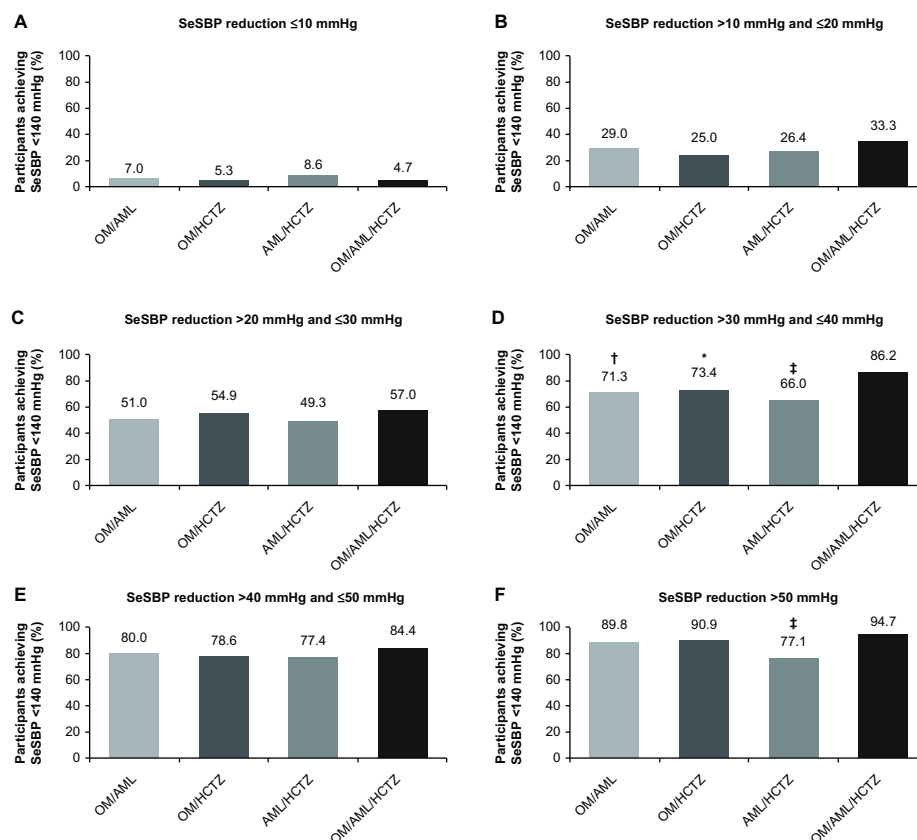
**Figure 4** Proportion of participants achieving a SeSBP target of <140 mmHg at week 12 (last observation carried forward).
**Notes:** Proportion of participants achieving a SeSBP target of <140 mmHg at week 12 (last observation carried forward) with a (**A**) ≤10 mmHg; (**B**) >10 mmHg and ≤20 mmHg; (**C**) >20 mmHg and ≤30 mmHg; (**D**) >30 mmHg and ≤40 mmHg; (**E**) >40 mmHg and ≤50 mmHg; and (**F**) >50 mmHg SeSBP reduction from baseline. Please see Figure 2 for the number of participants in each category. *P < 0.05; †P ≤ 0.01; ‡P ≤ 0.001, OM/AML/HCTZ versus dual-combination treatment.
**Abbreviations:** SeSBP, seated systolic blood pressure; OM, olmesartan medoxomil (40 mg); AML, amlodipine besylate (10 mg); HCTZ, hydrochlorothiazide (25 mg).

Across treatment groups, the most common TEAEs were dizziness (7.0%), headache (6.5%), peripheral edema (6.0%), and fatigue (5.4%). TEAEs that occurred in ≥5% of study participants in any treatment/SeSBP reduction category included these four events, as well as upper respiratory tract infection, nausea, and hypokalemia (low potassium) (Table 1). Peripheral edema was more prevalent in participants receiving AML 10 mg with or without OM 40 mg or HCTZ 25 mg, irrespective of SeSBP reduction; hypokalemia was more prevalent in participants receiving AML 10 mg/HCTZ 25 mg, irrespective of SeSBP reduction; and dizziness was more prevalent in participants receiving OM 40 mg/HCTZ 25 mg with or without AML 10 mg with a >40 mmHg reduction in SeSBP (Table 1). The prevalence of headache, upper respiratory tract infection, fatigue, and nausea did not appear to be related to treatment or degree of SeSBP reduction (Table 1). The prevalence of cough, hypotension, and orthostatic hypotension was low across treatments regardless of categorical SeSBP reduction (Table 1).

In the TRINITY study population, small changes were observed in each serum chemistry and hematologic parameter across the treatment groups (data not shown). Key chemistry parameters included alanine transaminase, aspartate transaminase, blood urea nitrogen, creatinine, sodium, potassium, and bicarbonate; key hematology parameters included hemoglobin, hematocrit, white blood cell count, and platelet count. These changes had no apparent relationship to treatment regimen and were not considered clinically significant.[11]

## Discussion

This prespecified analysis of a large, multicenter, randomized, parallel-group trial demonstrated the efficacy of triple-combination treatment with OM 40 mg/AML 10 mg/HCTZ 25 mg in lowering elevated SBP. Nearly 50% of participants randomized to triple-combination treatment achieved >40 mmHg and nearly 25% achieved >50 mmHg reduction in SeSBP. As a result, significantly more participants receiving triple-combination treatment achieved
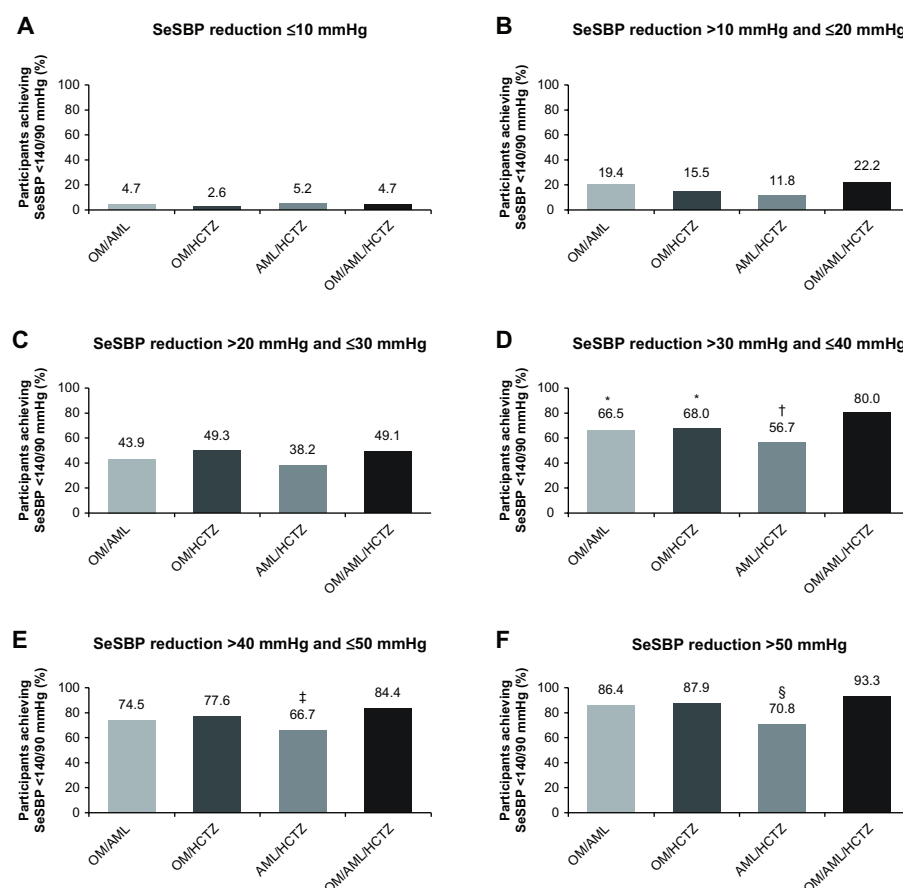
**Figure 5** Proportion of participants achieving a SeBP target of <140/90 mmHg at week 12 (last observation carried forward).
**Notes:** Proportion of participants achieving a SeBP target of <140/90 mmHg at week 12 (last observation carried forward) among participants with a (**A**) ≤10 mmHg; (**B**) >10 mmHg and ≤20 mmHg; (**C**) >20 mmHg and ≤30 mmHg; (**D**) >30 mmHg and ≤40 mmHg; (**E**) >40 mmHg and ≤50 mmHg; and (**F**) >50 mmHg SeSBP reduction from baseline. Please see Figure 2 for the number of participants in each category. *$P < 0.05$; †$P < 0.0001$; ‡$P ≤ 0.01$; §$P ≤ 0.001$, OM/AML/HCTZ versus dual-combination treatment.
**Abbreviations:** SeBP, seated blood pressure; OM, olmesartan medoxomil (40 mg); AML, amlodipine besylate (10 mg); HCTZ, hydrochlorothiazide (25 mg).

the SeSBP target of <140 mmHg. In addition, triple-combination treatment was well tolerated; the prevalence of TEAEs in the triple-combination treatment group was similar to that in the dual-combination treatment groups, both in participants with and without a >40 mmHg reduction in SeSBP.

As early as 1971, the Framingham Heart Study demonstrated that SBP more accurately reflects the risk of hypertension-associated complications than DBP; this finding has subsequently been confirmed in numerous evaluations.[3,6,12,13] A longitudinal assessment of >18,000 individuals found that the addition of SBP to a multivariate logistic regression model that already included DBP significantly enhanced the assessment of coronary heart disease mortality risk. However, the reverse was not true: addition of DBP to a model that already included SBP did not improve risk assessment.[13] Similarly, a meta-analysis of data from eight hypertension trials found that total mortality

was positively correlated with SBP but not with DBP in individuals ≥60 years of age.[3]

Similarly, improvements in cardiovascular outcomes have been shown to be more closely related to reductions in SBP than DBP.[8] In a meta-analysis of data from ten hypertension trials, active treatment decreased BP (weighted mean reduction: 21.9/13.7 mmHg) and significantly reduced cardiovascular events (cardiovascular events included stroke, coronary heart disease, and other fatal and nonfatal vascular disorders as defined in each trial).[8] However, this reduction in cardiovascular events was essentially identical and remained statistically significant across quartiles of DBP reduction, which indicates that the reduction in DBP had little, if any, effect on clinical outcomes independent of SBP reduction.[8]

Data from numerous clinical trials support the beneficial effects of reducing BP on cardiovascular and renal events, and some trials support the beneficial effects of reducing elevated SBP on cardiovascular and renal endpoints.[14–26]

**Table 1** Study participants with TEAEs by treatment and categorical SeSBP reduction

| Category | OM 40 mg/AML 10 mg | | OM 40 mg/HCTZ 25 mg | | AML 10 mg/HCTZ 25 mg | | OM 40 mg/AML 10 mg/HCTZ 25 mg | |
|---|---|---|---|---|---|---|---|---|
| | SeSBP reduction | | SeSBP reduction | | SeSBP reduction | | SeSBP reduction | |
| | ≤40 mmHg (n = 435) | >40 mmHg (n = 161) | ≤40 mmHg (n = 392) | >40 mmHg (n = 188) | ≤40 mmHg (n = 426) | >40 mmHg (n = 126) | ≤40 mmHg (n = 288) | >40 mmHg (n = 286) |
| All TEAEs* | 226 (52.0) | 82 (50.9) | 213 (54.3) | 106 (56.4) | 251 (58.9) | 74 (58.7) | 162 (56.3) | 173 (60.5) |
| Severe TEAEs | 18 (4.1) | 6 (3.7) | 11 (2.8) | 6 (3.2) | 14 (3.3) | 4 (3.2) | 11 (3.8) | 13 (4.5) |
| Drug-related TEAEs† | 99 (22.8) | 39 (24.2) | 81 (20.7) | 40 (21.3) | 126 (29.6) | 38 (30.2) | 76 (26.4) | 86 (30.1) |
| Drug-related serious adverse events | 1 (0.2) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Discontinuations | | | | | | | | |
| TEAEs | 6 (1.4) | 0 | 11 (2.8) | 1 (0.5) | 10 (2.3) | 1 (0.8) | 16 (5.6) | 7 (2.4) |
| Drug-related TEAEs | 4 (0.9) | 0 | 4 (1.0) | 1 (0.5) | 5 (1.2) | 0 | 11 (3.8) | 7 (2.4) |
| TEAEs that occurred in ≥5% of any group | | | | | | | | |
| Dizziness | 32 (7.4) | 7 (4.3) | 25 (6.4) | 24 (12.8) | 26 (6.1) | 5 (4.0) | 19 (6.6) | 35 (12.2) |
| Headache | 22 (5.1) | 10 (6.2) | 34 (8.7) | 13 (6.9) | 12 (2.8) | 7 (5.6) | 22 (7.6) | 18 (6.3) |
| Upper respiratory tract infection | 18 (4.1) | 8 (5.0) | 8 (2.0) | 10 (5.3) | 10 (2.3) | 4 (3.2) | 7 (2.4) | 9 (3.1) |
| Fatigue | 23 (5.3) | 11 (6.8) | 16 (4.1) | 15 (8.0) | 26 (6.1) | 10 (7.9) | 9 (3.1) | 15 (5.2) |
| Peripheral edema | 30 (6.9) | 12 (7.5) | 5 (1.3) | 1 (0.5) | 35 (8.2) | 11 (8.7) | 18 (6.3) | 26 (9.1) |
| Nausea | 4 (0.9) | 8 (5.0) | 13 (3.3) | 9 (4.8) | 9 (2.1) | 3 (2.4) | 9 (3.1) | 8 (2.8) |
| Hypokalemia | 1 (0.2) | 1 (0.6) | 2 (0.5) | 1 (0.5) | 16 (3.8) | 9 (7.1) | 2 (0.7) | 2 (0.7) |
| Other TEAEs | | | | | | | | |
| Cough | 3 (0.7) | 4 (2.5) | 10 (2.6) | 5 (2.7) | 9 (2.1) | 2 (1.6) | 6 (2.1) | 5 (1.7) |
| Hypotension | 0 | 0 | 2 (0.5) | 1 (0.5) | 0 | 0 | 4 (1.4) | 4 (1.4) |
| Orthostatic hypotension | 0 | 0 | 0 | 1 (0.5) | 0 | 0 | 0 | 2 (0.7) |

**Notes:** Values are n (%). *TEAEs were defined as adverse events that emerged during treatment (started on or after the first dose of double-blind medication) or that worsened relative to the pretreatment state. †Drug-related TEAEs were considered definitely, probably, or possibly related to randomized study medication.
**Abbreviations:** TEAE, treatment-emergent adverse event; SeSBP, seated systolic blood pressure; OM, olmesartan medoxomil; AML, amlodipine besylate; HCTZ, hydrochlorothiazide; n, number.

A meta-analysis of data from nearly 200,000 patients participating in 31 clinical trials found the risk of major cardiovascular events was reduced by 11.9% (95% confidence interval [CI]: 5.3%–18.0%) in individuals <65 years of age and 9.1% (95% CI: 3.6%–14.3%) in individuals ≥65 years of age for each 5 mmHg reduction in SBP.[26] As a result, current US guidelines recommend reducing SBP to <140 mmHg (<130 mmHg in patients with concomitant diabetes or chronic kidney disease).[2]

Studies have suggested that SBP may be more difficult to control than DBP. Although 90% of patients in ALLHAT and 91% of patients in the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) trial achieved DBP control, only 64% and 68% of patients in these trials, respectively, achieved SBP control despite the fact that >60% were taking ≥2 and some were taking ≥4 antihypertensive agents.[9,27]

As a result, resistant hypertension (the inability to achieve a patient's BP goal despite concurrent use of optimal doses of three antihypertensive agents of different classes, including a diuretic) is typically related to an inability to control SBP, not DBP.[28] Although the exact prevalence of resistant hypertension in the US is unknown,[28] it is clearly substantial. Overall, 30.1% of participants randomized to triple-combination treatment in the present trial did not achieve the SeBP target of <140/90 mmHg (26.4% did not achieve the SeSBP target of <140 mmHg) and could be classified as having resistant hypertension.

Figure 3 shows that participants with the largest SeSBP reductions also had the highest baseline SeSBP. However, there were some participants with high baseline SeSBP who did not achieve large SeSBP reductions. These participants, in addition to having elevated SeSBP, may have had demographic and baseline characteristics that resulted in variations of physiological responsiveness to treatment, which resulted in an inability to reach BP targets and a classification of resistant hypertension.

Treatment adherence is an important component of BP control. A recent evaluation using Medication Event Monitoring System caps to assess adherence found that mean SBP and DBP, respectively, were 11.6 mmHg and 7.7 mmHg higher (both $P < 0.001$) in patients after 7 days of poor (<60%) versus excellent (100%) adherence.[29] The use of multiple antihypertensive agents to reach BP targets may adversely affect adherence, leading to poorer BP control. This is especially relevant because most patients with hypertension will require two or more agents to reach their BP target, with approximately 25% of patients requiring three or more agents.[9,30–35] A retrospective evaluation of data from approximately 85,000 patients in the Kaiser Permanente system found an inverse correlation between the number of antihypertensive medications prescribed and adherence.[36] Consistent with this, several evaluations have shown that the use of fixed-dose, single-pill combination therapy to simplify the therapeutic regimen and reduce pill burden significantly improves adherence relative to free-dose combination therapy.[37–41]

Because most patients with hypertension (especially those >50 years of age) will reach their DBP goal once their SBP goal is reached, the treatment of hypertension should focus primarily on controlling SBP; SBP targets are typically more difficult to achieve than DBP targets, and SBP levels are more closely correlated with cardiovascular risk than DBP levels.[2] Single-pill combination therapy may increase patient adherence and enable more patients to achieve SBP targets. As shown in the present study, OM 40 mg/AML 10 mg/HCTZ 25 mg may be a safe and effective option in these patients.

## Acknowledgments

## Disclosure

Dr Sugimoto has received grant/research support from Daiichi Sankyo, Inc. Dr Chrysant has served as a consultant and speakers' bureau member for and received grant/research support and honoraria from Daiichi Sankyo, Inc. Dr Melino, Dr Lee, and Victor Fernandez are employees of Daiichi Sankyo, Inc. Dr Heyrman is a former employee of Daiichi Sankyo, Inc. The authors report no other conflicts of interest in this work.

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