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## Triple Antihypertensive Therapy With Amlodipine, Valsartan, and Hydrochlorothiazide A Randomized Clinical Trial

David A. Calhoun, Yves Lacourcière, Yann Tong Chiang, Robert D. Glazer

**Abstract**—Many patients with hypertension require  $\geq 3$  agents to achieve target blood pressure (BP). The efficacy/safety of the dual combinations of valsartan (Val)/hydrochlorothiazide (HCTZ) and amlodipine (Aml)/Val in hypertension are well established. This randomized, double-blind study evaluated the efficacy/safety of triple therapy with Aml/Val/HCTZ for moderate or severe hypertension (mean sitting systolic BP:  $\geq 145$  mm Hg; mean sitting diastolic BP:  $\geq 100$  mm Hg). The study included a single-blind, placebo run-in period, followed by double-blind treatment for 8 weeks; patients were randomly assigned to 1 of 4 groups titrated to Aml/Val/HCTZ 10/320/25 mg, Val/HCTZ 320/25 mg, Aml/Val 10/320 mg, or Aml/HCTZ 10/25 mg once daily. Dual-therapy recipients received half of the target doses of both agents for the first 2 weeks, titrating to target doses during week 3. Those on triple therapy received Val/HCTZ 160.0/12.5 mg during week 1, Aml/Val/HCTZ 5.0/160.0/12.5 mg during week 2, and target doses of all 3 of the agents during week 3. Of the 4285 patients enrolled, 2271 were randomly assigned to treatment, and 2060 completed the study. Triple therapy was significantly superior to all of the dual therapies in reducing mean sitting systolic BP and mean sitting diastolic BP from baseline to end point (all  $P < 0.0001$ ). Significantly more patients on triple therapy achieved overall BP control ( $< 140/90$  mm Hg;  $P < 0.0001$ ) and systolic and diastolic control ( $P \leq 0.0002$ ) compared with each dual therapy. Aml/Val/HCTZ was well tolerated. The benefits of triple therapy over dual therapy were observed regardless of age, sex, race, ethnicity, or baseline mean sitting systolic BP. In conclusion, this study demonstrates the efficacy/safety of treating moderate and severe hypertension with Aml/Val/HCTZ 10/320/25 mg. (*Hypertension*. 2009;54:32-39.)

**Key Words:** amlodipine ■ valsartan ■ hydrochlorothiazide ■ hypertension ■ triple therapy

Hypertension treatment guidelines recommend a target blood pressure (BP) goal of  $< 140/90$  mm Hg for uncomplicated hypertension. Target goals are lower ( $< 130/80$  mm Hg) for patients with hypertension complicated by diabetes mellitus or renal disease or for those considered at high risk (eg, history of stroke or myocardial infarction).<sup>1,2</sup> To facilitate attainment of these target goals in at-risk patients, the guidelines recommend dual therapy as the initial treatment.<sup>1,2</sup> However, despite extensive evidence of the negative effects of poorly controlled BP and the numerous antihypertensive agents available, only approximately one third of hypertensive patients achieve adequate BP control in the United States.<sup>3</sup> Because of the multifactorial nature of hypertension, most patients require treatment with  $> 1$  antihypertensive agent to achieve target pressure,<sup>4</sup> with many patients requiring  $\geq 3$  agents.<sup>5,6</sup>

Antihypertensive regimens that include  $\geq 2$  agents with complementary mechanisms of action may result in greater reductions in BP than the single-agent components. For example, the use of a calcium channel blocker, an angiotensin

receptor blocker, and a thiazide diuretic represents a logical choice for combination therapy. A calcium channel blocker inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle, an angiotensin receptor blocker inhibits angiotensin II-mediated vasoconstriction and renal sodium retention, and a thiazide diuretic reduces intravascular volume and total body sodium. In addition to potential efficacy benefits when used in combination, one antihypertensive agent may attenuate certain adverse effects of another.<sup>7,8</sup> For example, in addition to valsartan (Val) and hydrochlorothiazide (HCTZ) providing a greater antihypertensive effect in combination over either agent alone, Val attenuates the HCTZ-induced hypokalemia.<sup>9</sup> The BP-lowering effects of the combination of Val and amlodipine (Aml) also are greater than either monotherapy, and rates of peripheral edema are lower with the combination than with Aml alone.<sup>10</sup>

The efficacy and safety of the combinations of Val/HCTZ and Aml/Val are well established,<sup>9-17</sup> with each combination available in a single-pill formulation. The convenience and

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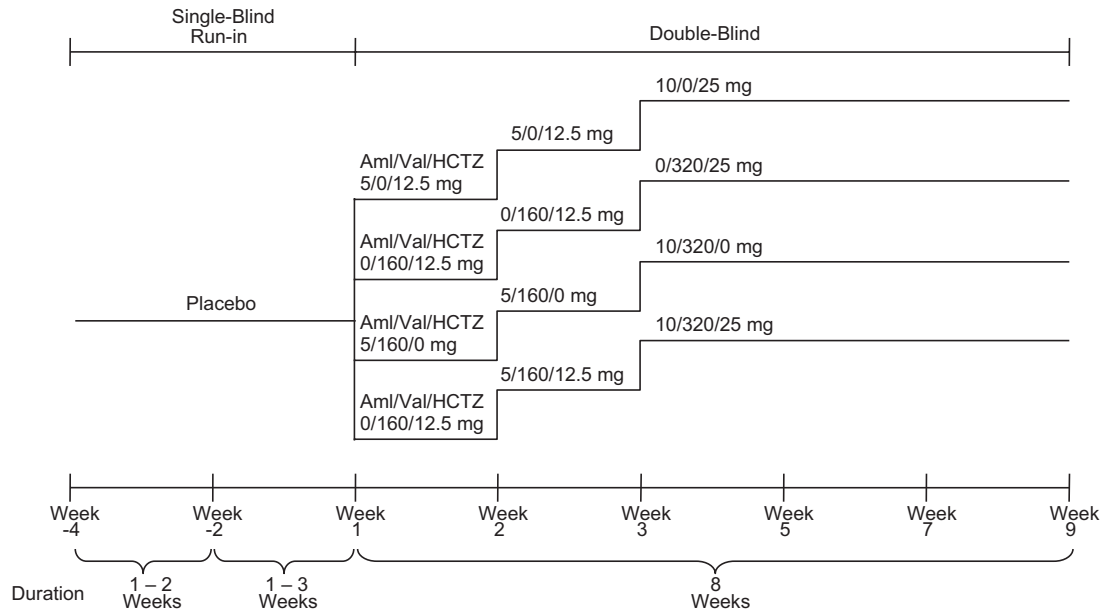


Figure 1. Study design.

simplicity of treatment with a single pill may improve treatment adherence and persistence.<sup>18</sup> This is especially important among patients with hypertension.<sup>19</sup> Reducing pill burden also may improve the psychological well being of patients. Triple therapy with Aml/Val/HCTZ may prove superior to dual therapy in the treatment of hypertension. If so, combining these agents into a single-pill formulation would provide enhanced efficacy while retaining ease of administration.

The purpose of the current study was to evaluate the efficacy and safety of triple therapy Aml/Val/HCTZ 10/320/25 mg compared with each of the dual components (Val/HCTZ 320/25 mg, Aml/Val 10/320 mg, and Aml/HCTZ 10/25 mg) in patients with moderate or severe hypertension.

Methods

Study Design

This study was a multinational, randomized, double-blind, parallel-group trial. The study protocol was approved by the independent ethics committee or institutional review board for each center, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All of the patients provided written informed consent before random assignment.

Patients

Eligible patients were between 18 and 85 years of age with moderate or severe (grade 2 or 3<sup>2</sup>; stage 2<sup>1</sup>) hypertension (mean sitting systolic BP [SBP; MSSBP] ≥145 mm Hg and mean sitting diastolic BP [DBP; MSDBP] ≥100 mm Hg) at random assignment. Patients discontinued previous antihypertensive medications after ≥1 week of placebo run-in. Patients with severe hypertension (MSSBP ≥180 mm Hg or MSDBP ≥110 mm Hg) were randomly assigned immediately. Those who did not meet these criteria were randomly assigned after 2 to 3 weeks of placebo if they achieved MSSBP ≥145 mm Hg and MSDBP ≥100 mm Hg. Patients with MSSBP ≥200 mm Hg or MSDBP ≥120 mm Hg were discontinued.

Women were required to be postmenopausal for 1 year, to be surgically sterile, or to be using an effective method of birth control other than hormonal contraceptives. Patients were excluded at screening if they were receiving ≥4 antihypertensive agents. Patients

also were excluded at screening if they were receiving 3 antihypertensive agents with an MSSBP/MSDBP of ≥140/90 mm Hg; 2 antihypertensive agents with an MSSBP/MSDBP of ≥180/110 mm Hg; or no antihypertensive agents with an MSSBP/MSDBP of <140/90 mm Hg. Additional exclusion criteria included a history of hypersensitivity to any of the study drugs; history of hypertensive encephalopathy, cerebrovascular accident, transient ischemic attack, myocardial infarction, or any revascularization procedure; second- or third-degree heart block; angina pectoris; significant arrhythmia or valvular heart disease; type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus; significant pancreatic, hepatic, or renal disease; serum sodium and/or serum potassium levels <132.0 mmol/L and <3.2 mmol/L, respectively; or concomitant use of medications known to significantly affect BP.

Study Design

This randomized, double-blind, parallel-group, active-controlled study was conducted in 15 countries. The study design is shown in Figure 1. The study included a single-blind, placebo run-in period for a maximum of 4 weeks followed by an 8-week, double-blind treatment period. For patients on an antihypertensive medication at screening that required gradual withdrawal, a 1-week withdrawal period preceded the placebo run-in period.

Patients were provided with an Omron home BP monitor (model HEM705CP) to measure SBP and DBP at home twice daily during the placebo run-in period. They were instructed to call the research site for consultation and to schedule an office visit to determine eligibility if a home BP reading reached ≥180 mm Hg for SBP and/or ≥110 mm Hg for DBP. Patients who met the BP criteria at their clinic visit (MSSBP ≥145 mm Hg and <200 mm Hg and MSDBP ≥100 mm Hg and <120 mm Hg) were randomly assigned (1:1:1:1) to 1 of 4 treatment groups of double-blind treatment: Aml/Val/HCTZ 10/320/25 mg, Val/HCTZ 320/25 mg, Aml/Val 10/320 mg, or Aml/HCTZ 10/25 mg once daily. Patients were discontinued if they did not meet the BP criteria after a total of 4 weeks on placebo.

The first 2 weeks postrandomization were a 2-stage forced-titration period with lower doses of study medications (Figure 1). From the start of the third week through the end of the trial (a total of 6 weeks), all of the treatment groups received their final doses of study drug. Downward dose titration of study drug was not permitted at any time.

Beginning at screening and continuing throughout the study, each patient took 2 tablets and 2 capsules at ≈8 AM, except on days when

clinic visits were scheduled. Val was administered as 160.0-mg tablets, HCTZ as 12.5-mg or 25.0-mg capsules, and Aml as 5.0-mg or 10.0-mg capsules. Placebo was administered as either a tablet or capsule to maintain blinding. The identity of the treatments was concealed by the use of study drugs that appeared identical in packaging, labeling, and schedule of administration. In addition, the appearance, weight, and odor of each study drug and its matching placebo were identical. Compliance was assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient.

### Efficacy Assessments

Automated arterial BP determinations were made in the clinic using an Omron BP monitor and an appropriate cuff size, in accordance with published guidelines.<sup>20</sup> BP was measured at screening and at each visit through the end of the study. Whenever possible, the same staff member made BP measurements for a given patient at each visit. At study entry, BP was measured in both arms, and the arm with the higher DBP was used for the first and all of the subsequent visits. At each visit, after the patient had been sitting for 5 minutes with both feet on the floor, SBP and DBP were measured 3 times, at 2-minute intervals. BP measurements were performed at trough (23 to 26 hours postdose). MSSBP and MSDBP were calculated as the mean of the 3 BP measurements.

### Safety Assessments

Key safety assessments included adverse events (AEs), serious AEs, and laboratory parameters (hematology and biochemistry).

### Sample Size

A total sample size of 2024 completed patients was planned for this study, assuming 2252 patients were randomly assigned (563 patients per group) and a maximum dropout rate of 10%. This sample size would provide 90% power at a 2-sided significance level of 0.025 to obtain statistical significance for triple therapy versus the 3 dual therapies for change from baseline in MSSBP and MSDBP, assuming a true treatment difference between triple therapy and each dual therapy of 2.0 and 3.5 mm Hg, respectively, and a common SD of 8.0 and 14.0 mm Hg, respectively.

### Statistical Analyses

Efficacy analyses were performed using the intent-to-treat population, which included all of the randomly assigned patients who had a baseline and  $\geq 1$  postbaseline assessment of the efficacy variables MSSBP and MSDBP. The safety population included all of the patients who received  $\geq 1$  dose of double-blind study drug. To avoid potential problems in the statistical analysis because of small centers, 4 regions were prespecified before unblinding treatment codes for analyses.

The primary efficacy outcome was change from baseline to end point (last observation carried forward) in MSSBP and MSDBP. Secondary efficacy outcomes included change from baseline to weeks 5, 7, and 9 in MSSBP and MSDBP, SBP control (MSSBP  $< 140$  mm Hg), DBP control (MSDBP  $< 90$  mm Hg), and overall BP control (MSSBP/MSDBP  $< 140/90$  mm Hg) rates at end point and at weeks 5, 7, and 9.

To assess the superiority of triple therapy compared with the dual therapies, a 2-way ANCOVA was used, with treatment and region as factors and baseline MSSBP (or MSDBP) as a covariate. Hochberg's multiple-testing step-up procedure<sup>21</sup> was used to control the overall type I error rate at the 2-sided 0.05 level for the 2 primary efficacy variables, MSSBP and MSDBP. Within-treatment analyses of BP changes from baseline were performed using 1-sample *t* tests. Comparisons of MSSBP, MSDBP, and overall control rates for triple therapy compared with the dual therapies were performed using a logistic regression model, with treatment and region as factors.

Primary and secondary efficacy variables also were summarized by subgroups, including age group ( $< 65$  years or  $\geq 65$  years), sex (male or female), and race (white, black, Asian, Native American, Pacific Islander, or other). In addition, a posthoc analysis of the

primary efficacy variable was conducted based on MSSBP at baseline ( $< 180$  mm Hg or  $\geq 180$  mm Hg) and on subgroups by ethnicity (Hispanic/Latino or non-Hispanic/Latino [including Chinese, Indian subcontinent, Japanese, mixed ethnicity, or other]). Between-treatment comparisons for these subgroups were performed the same way as for the intent-to-treat population.

## Results

### Patients

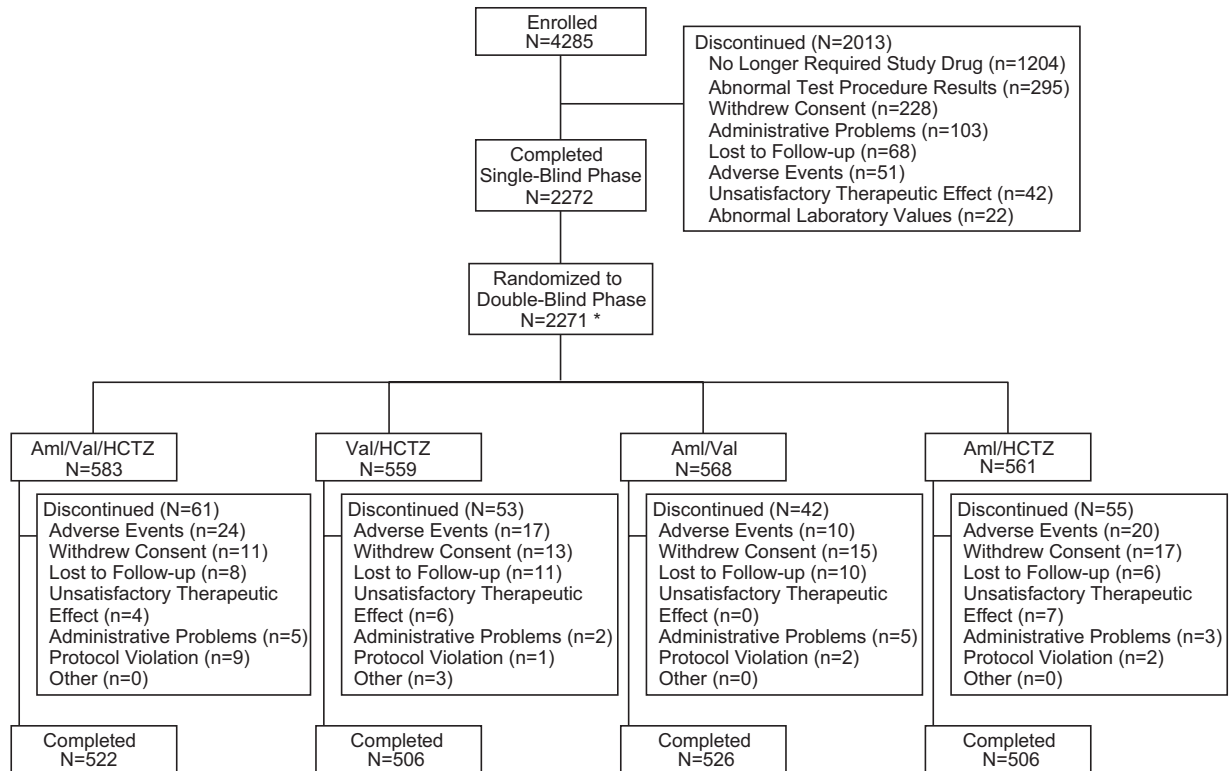
Of the 4285 patients enrolled, 2271 were randomly assigned to double-blind treatment, and 2060 completed the study (Figure 2). One patient who completed the placebo run-in period was excluded from all of the analyses, because treatment assignment was unknown. The completion rates were similar across treatment groups. The most common reasons for discontinuation from the placebo run-in period included patient condition no longer required study drug (28.1%), abnormal test procedure results (6.9%), and withdrawal of consent (5.3%). The most common reasons for discontinuation from the double-blind treatment period included AEs (3.1%), withdrawal of consent (2.5%), and lost to follow-up (1.5%). The intent-to-treat and safety populations were composed of 2236 and 2268 patients, respectively. Efficacy data from 1 site (12 randomly assigned patients) was excluded from all of the efficacy analyses because of the discovery of several protocol irregularities and subsequent ceasing of all of the trial-related activities at this site.

Demographic and baseline characteristics were generally comparable among treatment groups (Table 1). Approximately 72% of the randomly assigned patients were white, and 55% were men. The mean age of patients was 53 years, with 14% aged  $\geq 65$  years. MSSBP/MSDBP was 169.9/106.5 mm Hg at baseline, and the mean duration of hypertension was  $\approx 9$  years. Approximately 10% of patients were diabetic, and 26% had a Hispanic/Latino ethnicity. Before enrollment, the most frequently reported classes of antihypertensive agents being taken by participants included plain angiotensin-converting enzyme inhibitors (30.2%), dihydropyridine derivatives (18.1%), plain thiazides (17.3%), plain angiotensin II antagonists (16.4%), and selective  $\beta$ -blocking agents (12.5%).

### Change From Baseline in MSSBP and MSDBP

Least-square mean changes from baseline in SBP and DBP are shown in Table 2. The greatest reductions in MSSBP and MSDBP were observed in the triple-therapy Aml/Val/HCTZ group (39.68 mm Hg and 24.74 mm Hg, respectively). Between-treatment comparisons showed that triple therapy was statistically superior to all 3 of the dual therapies in reducing both MSSBP and MSDBP from baseline to end point (all  $P < 0.0001$ ). Results of between-treatment comparisons at weeks 5, 7, and 9 were similar to those achieved at the end point (all  $P < 0.0001$ ).

In all of the treatment groups, the full BP-lowering effect was seen after 2 weeks (ie, week 5) at maximal dose (Figure 3). Starting at week 5, triple therapy was significantly superior to each dual therapy in BP reduction.



**Figure 2.** Patient disposition. \*One additional patient was randomly assigned but was excluded from all of the analyses because treatment assignment was unknown.

**Control Rates**

At each assessment after week 3, a significantly greater proportion of patients receiving triple therapy achieved overall BP control (<140/90 mm Hg) compared with those receiving any of the dual therapies (all  $P < 0.0001$ ). At end point, 70.8% of patients in the triple-therapy group achieved control, compared with 48.3% for Val/HCTZ, 54.1% for Aml/Val, and 44.8% for Aml/HCTZ (all  $P < 0.0001$ ). In

addition, systolic control rates (<140 mm Hg) and diastolic control rates (<90 mm Hg) were significantly greater at each assessment for triple therapy compared with each of the dual therapies (all  $P \leq 0.0002$ ; data not shown).

**Subgroup Analyses**

Subgroup analyses of change from baseline to end point in mean sitting BPs and control rates were conducted for age

**Table 1. Demographic and Baseline Characteristics by Treatment (Randomized Population)**

Characteristic	Aml/Val/HCTZ 10/320/25 mg (n=583)	Val/HCTZ 320/25 mg (n=559)	Aml/Val 10/320 mg (n=568)	Aml/HCTZ 10/25 mg (n=561)	Total (N=2271)
Sex, n (%)					
Male	316 (54.2)	303 (54.2)	319 (56.2)	317 (56.5)	1255 (55.3)
Female	267 (45.8)	256 (45.8)	249 (43.8)	244 (43.5)	1016 (44.7)
Mean (SD) age, y	53.3 (10.3)	53.1 (10.4)	52.8 (10.3)	53.6 (10.1)	53.2 (10.3)
Age group, n (%), y					
<65	501 (85.9)	483 (86.4)	492 (86.6)	478 (85.2)	1954 (86.0)
≥65	82 (14.1)	76 (13.6)	76 (13.4)	83 (14.8)	317 (14.0)
Race, n (%)					
White	420 (72.0)	412 (73.7)	403 (71.0)	392 (69.9)	1627 (71.6)
Black	98 (16.8)	93 (16.6)	91 (16.0)	107 (19.1)	389 (17.1)
Other	65 (11.1)	54 (9.7)	74 (13.0)	62 (11.1)	255 (11.2)
Ethnicity, n (%)					
Hispanic/Latino	152 (26.1)	141 (25.2)	148 (26.1)	147 (26.2)	588 (25.9)
Non-Hispanic/Latino	431 (73.9)	418 (74.8)	420 (73.9)	414 (73.8)	1683 (74.1)
Mean (SD) MSSBP, mm Hg	169.6 (14.5)	169.5 (13.8)	169.6 (13.7)	170.8 (14.3)	169.9 (14.1)
Mean (SD) MSDBP, mm Hg	106.4 (5.1)	106.2 (5.1)	106.6 (5.1)	107.1 (5.1)	106.5 (5.1)

**Table 2. Between-Treatment Comparisons for Change From Baseline to End Point in Mean Sitting BP (Intent-to-Treat Population)**

Treatment*	LSM Change From Baseline	LSM Difference in Change From Baseline (SE)	P	Hochberg Adjusted P
SBP, mm Hg				
Aml/Val/HCTZ 10/320/25 mg	-39.7			<0.0001
Val/HCTZ 320/25 mg	-32.0	-7.6 (0.85)	<0.0001	
Aml/Val 10/320 mg	-33.5	-6.2 (0.85)	<0.0001	
Aml/HCTZ 10/25 mg	-31.5	-8.2 (0.85)	<0.0001	
DBP, mm Hg				
Aml/Val/HCTZ 10/320/25 mg	-24.7			<0.0001
Val/HCTZ 320/25 mg	-19.7	-5.1 (0.54)	<0.0001	
Aml/Val 10/320 mg	-21.5	-3.3 (0.54)	<0.0001	
Aml/HCTZ 10/25 mg	-19.5	-5.3 (0.54)	<0.0001	

LSM indicates least square means.

\*n=571 in the Aml/Val/HCTZ group, 553 in the Val/HCTZ group, 558 in the Aml/Val group, and 554 in the Aml/HCTZ group.

(<65 and  $\geq$ 65 years), sex, race (white and black only, because the numbers of patients in other racial subgroups were small), or ethnicity (Hispanic/Latino and non-Hispanic/Latino). For both MSSBP and MSDBP, triple therapy was numerically superior to, and for the majority of the comparisons statistically superior to, each of the dual therapies regardless of age, sex, race, and ethnicity. Significantly greater proportions of patients treated with triple therapy achieved overall BP control compared with each dual therapy in both age groups, both sexes, both racial subgroups, and

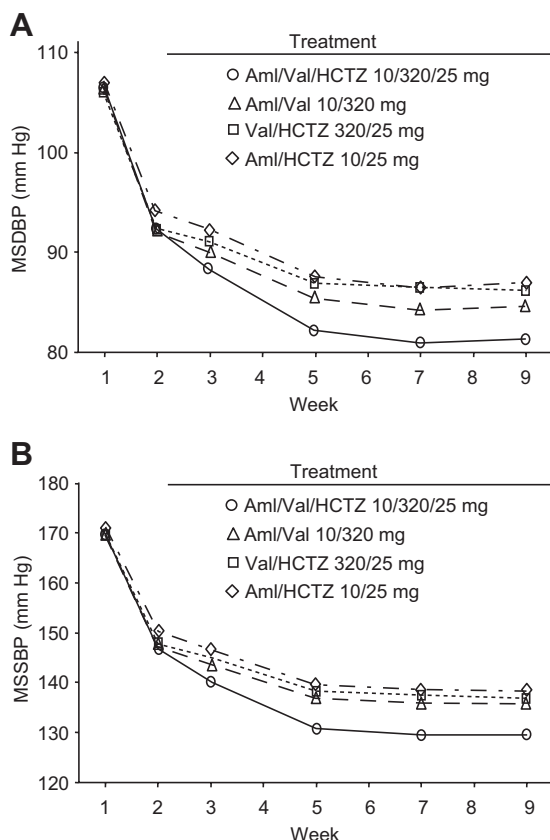
both ethnic subgroups (data not shown). In addition, triple therapy was statistically superior to each of the dual therapies in change from baseline to end point in both MSSBP and MSDBP, regardless of baseline MSSBP (<180 mm Hg or  $\geq$ 180 mm Hg; all  $P<0.01$ ; Figure 4).

### Safety

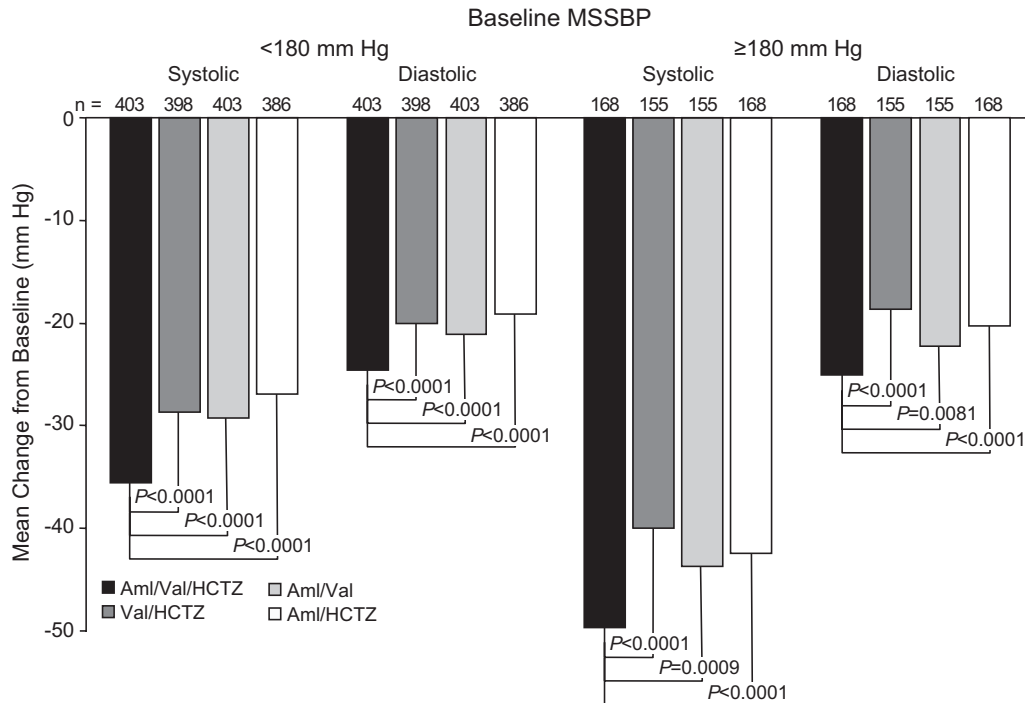
The frequencies of patients reporting  $\geq$ 1 AE during the double-blind treatment phase were similar across treatment groups, ranging from 45% to 48%. The majority of AEs were categorized as mild to moderate in intensity. The most frequently reported AEs were peripheral edema (5.7%), headache (5.4%), and dizziness (5.2%; Table 3). Dizziness occurred more frequently with triple therapy (7.7%) and Val/HCTZ (7.0%) than with Aml/Val (2.3%) or Aml/HCTZ (3.9%). Peripheral edema occurred less frequently with triple therapy (4.5%) and Val/HCTZ (0.9%) compared with Aml/HCTZ (8.9%) or Aml/Val (8.5%). Overall, there was a low incidence of other AEs related to, or potentially related to, low BP across treatment groups, eg, hypotension ( $\leq$ 1.5%), syncope (<1.0%), and postural dizziness, orthostatic hypotension, and exertional dizziness (each <0.5%).

There were no deaths during the study. Less than 1% of patients experienced a serious AE; all occurred at similar frequencies across treatment groups. The incidence of the most frequently reported AEs leading to study discontinuation by treatment group (Aml/Val/HCTZ, Val/HCTZ, Aml/Val, Aml/HCTZ) was dizziness (1.0%, 1.1%, 0.4%, and 0.2%, respectively), hypotension (0.7%, 1.1%, 0%, and 0%, respectively), and peripheral edema (0.2%, 0%, 0.4%, and 0.9%, respectively).

Laboratory changes were consistent with the known biochemical effects of Aml, Val, and HCTZ; eg, increases in mean blood urea nitrogen were observed in all of the treatment groups, and increases in mean uric acid occurred in the treatment groups that received HCTZ. Mean potassium decreased in all of the groups receiving HCTZ, with the greatest decrease in the Aml/HCTZ group ( $-0.39$  mmol/L) and smaller decreases in the Aml/Val/HCTZ ( $-0.16$  mmol/L) and the Val/HCTZ ( $-0.08$  mmol/L) groups. A slight increase in potassium was observed in the Aml/Val group (0.04 mmol/L).



**Figure 3.** Mean sitting DBP (A) and SBP (B) by treatment and week.



**Figure 4.** Between-treatment comparisons for change from baseline to end point in mean sitting BP (mm Hg) by baseline MSSBP. Data presented are least-square mean changes.

Mean changes from baseline in other biochemistry tests were relatively small, with no clinically relevant differences among treatment groups.

### Discussion

This is the first large, randomized, double-blind, multicenter study to assess the efficacy and safety of triple therapy for the treatment of moderate or severe hypertension. Triple therapy with Aml/Val/HCTZ produced robust reductions in both MSSBP and MSDBP that were statistically superior to all of the component dual therapies. The observed 3.3- to 5.3-mm Hg decreases in MSDBP in favor of triple therapy are clinically significant, because even small reductions in DBP are associated with substantial decreases in cardiovascular risk. For example, a 2-mm Hg decrease in DBP has been estimated to reduce the risk of coronary heart disease by 6%

and stroke and transient ischemic attack by 15%.<sup>22</sup> In the Valsartan Antihypertensive Long-term Use Evaluation Trial, a small difference in BP reduction ( $\approx 4/2$  mm Hg) between active treatments was associated with a significant difference in the incidences of stroke and all-cause mortality and time to first cardiac event.<sup>23</sup>

Only approximately one third of patients treated for hypertension achieve BP control.<sup>24</sup> The majority of controlled patients require combination therapy,<sup>4</sup> frequently with  $\geq 3$  agents.<sup>5,6</sup> In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial,<sup>5</sup> 23% of patients at BP goal after 5 years were receiving  $\geq 3$  agents. In the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension Trial, where all of the patients were started on dual antihypertensive therapy,<sup>6</sup> 26% of patients needed  $\geq 1$  additional drug to reach the BP

**Table 3. AEs ( $\geq 2\%$  in Triple-Therapy Group), Regardless of Study-Drug Relationship (Safety Population)**

Preferred Term	Aml/Val/HCTZ 10/320/25 mg (n=582), n (%)	Val/HCTZ 320/25 mg (n=559), n (%)	Aml/Val 10/320 mg (n=566), n (%)	Aml/HCTZ 10/25 mg (n=561), n (%)	Total (n=2268), n (%)
Any preferred term	263 (45.2)	253 (45.3)	254 (44.9)	271 (48.3)	1041 (45.9)
Dizziness	45 (7.7)	39 (7.0)	13 (2.3)	22 (3.9)	119 (5.2)
Peripheral edema	26 (4.5)	5 (0.9)	48 (8.5)	50 (8.9)	129 (5.7)
Headache	25 (4.3)	30 (5.4)	28 (4.9)	39 (7.0)	122 (5.4)
Dyspepsia	13 (2.2)	5 (0.9)	6 (1.1)	2 (0.4)	26 (1.1)
Fatigue	13 (2.2)	15 (2.7)	12 (2.1)	8 (1.4)	48 (2.1)
Muscle spasms	13 (2.2)	7 (1.3)	7 (1.2)	5 (0.9)	32 (1.4)
Back pain	12 (2.1)	13 (2.3)	5 (0.9)	12 (2.1)	42 (1.9)
Nasopharyngitis	12 (2.1)	13 (2.3)	13 (2.3)	12 (2.1)	50 (2.2)
Nausea	12 (2.1)	7 (1.3)	10 (1.8)	12 (2.1)	41 (1.8)

target during the initial 6 months. In the African American Study of Kidney Disease and Hypertension and the International Verapamil-Trandolapril Study, the percentage of patients requiring  $\geq 3$  agents during treatment to BP goal was even higher, ranging from 42% to 52%.<sup>25,26</sup>

In the recent Simplified Treatment Intervention to Control Hypertension Trial, triple therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, calcium channel blocker, and thiazide diuretic was the third step in a 4-step algorithm that included initial therapy with a low-dose, single-pill dual combination (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a diuretic) in 45 family practices.<sup>27</sup> At 6 months, the proportion of patients who achieved target BP was significantly higher in practices assigned to the algorithm approach compared with a conventional guideline (ie, Canadian Hypertension Education Program) approach (64.7% versus 52.7%;  $P=0.026$ ). In our present study in moderate or severe hypertension, 71% of patients receiving triple therapy had their BP controlled ( $<140/90$  mm Hg) compared with 45% to 54% for dual therapies ( $P<0.0001$ ). The full BP-lowering effect was seen after 2 weeks at maximal dose.

Achieving adequate BP can be extremely challenging in certain populations, including blacks, elderly, and diabetic patients with severe systolic hypertension.<sup>1</sup> Difficulty in attaining BP control in black patients may be attributed to a decreased response to monotherapy with drugs that suppress the renin-angiotensin-aldosterone system compared with white patients.<sup>28</sup> In elderly patients, poor BP control may be attributed to an increased incidence of systolic hypertension in this population,<sup>29</sup> coupled with an increased reluctance of physicians to treat systolic hypertension compared with diastolic hypertension.<sup>30</sup> In the current study, triple therapy with Aml/Val/HCTZ produced reductions in MSSBP and MSDBP that were numerically superior to, and for the majority of the comparisons statistically superior to, each of the dual therapies regardless of age, sex, race, or ethnicity.

The present study confirms the benefits of using drugs with complementary mechanisms of action to treat hypertension. Triple therapy with Aml/Val/HCTZ improved BP control significantly better than any of the dual therapies and was well tolerated. In fact, the Val component of the triple therapy was able to attenuate the diuretic-induced hypokalemia. These results are consistent with previous studies in which hypokalemia was lower with the combination of Val/HCTZ than with HCTZ monotherapy (1.8% to 6.1% versus 7.1% to 13.3%).<sup>9</sup>

### Perspectives

The current study demonstrated the efficacy and safety of treating moderate or severe hypertension with triple therapy consisting of Aml/Val/HCTZ 10/320/25 mg. Initial treatment of hypertension with a dual-combination agent with complementary mechanisms of action may allow BP goals to be realized more quickly than adding single entities slowly or at lower doses over multiple visits.<sup>6</sup> The use of combination therapy in our study population is consistent with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

and European Society of Hypertension and of the European Society of Cardiology treatment guidelines, which recommend combination therapy in patients whose BP is  $>20$  mm Hg above the systolic goal or  $>10$  mm Hg above the diastolic goal.<sup>1,2</sup> We found that full doses of Aml, Val, and HCTZ can be safely administered concomitantly using a simple and rapid up-titration schedule on the basis of initial therapy with a dual agent. Because delaying the time to BP control is a risk factor for cardiovascular events,<sup>23,31</sup> a therapeutic option that acts quickly and safely would be of great value. The availability of single-pill combinations may be an additional benefit in that it has the potential to greatly improve patient adherence compared with administration of multiple pills,<sup>32</sup> thereby having the potential to facilitate the distinguishing of true resistant hypertension from a lack of BP control because of nonadherence. Triple therapy, therefore, holds promise for those patients whose BP remains uncontrolled after dual-combination therapy.

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