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ORIGINAL RESEARCH

Amlodipine/Valsartan/Hydrochlorothiazide Triple Combination Therapy in Moderate/Severe Hypertension: Secondary Analyses Evaluating Efficacy and Safety

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ABSTRACT

Introduction: An 8-week trial of amlodipine/valsartan/hydrochlorothiazide (Aml/Val/HCTZ) for moderate or severe hypertension demonstrated more-pronounced blood pressure (BP)-lowering effects compared with dual-component therapies. To elucidate the effects of time and baseline BP on the observed responses, exploratory analyses were performed. ***Methods:*** Patients aged 18-85 years with mean sitting systolic BP (MSSBP) 145 to <200 mmHg and mean sitting diastolic BP (MSDBP) 100 to <120 mmHg were randomized to Aml 10 mg/Val 320 mg/HCTZ 25 mg; Val 320 mg/HCTZ 25 mg; Aml 10 mg/Val 320 mg; or Aml 10 mg/HCTZ 25 mg. During the first 2 weeks, regimens were force-titrated in two stages. ***Results:*** All least-square mean reductions in MSSBP and MSDBP (baseline to Week 3 and end of study) were significantly greater with triple therapy than with each dual therapy in the overall population and the severe systolic subgroup (baseline MSSBP ≥180 mmHg; except vs. Aml 10 mg/Val 320 mg at Week 3). At Week 3, more patients on triple therapy achieved MSSBP reductions of ≥60, ≥50, ≥40, ≥30, and ≥20 mmHg (2.5%, 9.7%, 23.2%, 46.9% and 74.5%, respectively) than those on dual therapy (1.1%-2%, 5.6%-5.9%, 14.5%-16.7%, 33.5%-39.1%, and 58.8%-65.5%, respectively); this was also true at study endpoint. End-of-study MSSBP reductions were greater in triple-therapy recipients who had higher (vs. lower) baseline MSSBPs. LSM reductions ranged from 27.2 mmHg for baseline MSSBP 145 to <150 mmHg, to 49.6 mmHg for baseline MSSBP ≥180 mmHg. All treatments were well tolerated regardless of baseline MSSBP. ***Conclusion:*** Aml 10 mg/Val 320 mg/HCTZ 25 mg triple therapy is highly effective in reducing BP compared with dual components early in therapy, and systolic BP-lowering effects were proportionate to hypertension severity.

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INTRODUCTION

The effective treatment of moderate or severe hypertension often requires the use of multiple antihypertensive agents from different drug classes.[1-5] The blood pressure (BP)-lowering benefits of dual antihypertensive combinations—including the calcium channel blocker, amlodipine (Aml), plus the angiotensin II receptor blocker valsartan, (Val)—are well documented for patients in whom monotherapy proved inadequate or as initial therapy for Stage 2 or Grades 2/3 hypertension.[6-14] In the latter setting, clinical practice guidelines, developed by the Joint National Committee and The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and of the European Society of Cardiology, recommend first-line, dual-combination therapy to increase the likelihood of rapid BP reduction relative to monotherapy.[1,15] The availability of various single-pill antihypertensive combinations offers the potential for increased patient adherence/compliance to therapy,[1,16] which would be expected to translate into both clinical and economic benefits, such as improved BP control and lower rates of associated cardiorenal complications.

For patients who do not respond to dual therapy, the addition of a third drug is usually necessary. It has been estimated that approximately 25% of hypertensive patients are prescribed three or more drugs to control BP.[17] The single-pill combination of Aml/Val/hydrochlorothiazide (HCTZ) was approved recently in the United States. In an 8-week, multicenter, randomized, four-arm trial of Aml 10 mg/Val 320 mg/HCTZ 25 mg (Aml/Val/HCTZ) versus each of its dual components for moderate or severe hypertension, the triple therapy was significantly more effective than any of the three dual regimens in reducing both systolic BP (SBP; $P<0.0001$) and diastolic BP (DBP; $P<0.0001$) and in achieving BP <140/90 mmHg at study endpoint (70.8% of patients who received triple therapy vs. 44.8% to 54.1% of those who received dual therapies; $P<0.0001$).[18] Triple therapy was well tolerated compared with dual therapy.[18]

In assessing the efficacy of a given antihypertensive regimen, clinical studies typically focus on change from baseline in mean BP in the entire study population at endpoint. However, the magnitude of treatment response may be influenced by various factors including the severity of hypertension and the dose and duration of treatment. Efficacy also can be summarized using a categorical approach of analyzing the proportion of patients responding to therapy based on different ranges of reductions in BP. This report summarizes exploratory analyses from the aforementioned randomized clinical trial of Aml/Val/HCTZ.[18] The aim of these analyses was to evaluate the relative efficacy of triple therapy vs. dual therapy using different efficacy criteria, to investigate the effect of baseline BP levels on treatment response, and to explore the early treatment effects of triple therapy. These analyses are particularly relevant for gaining a better understanding of the patient populations likely to benefit from triple therapy and the expected treatment responses.

MATERIALS AND METHODS

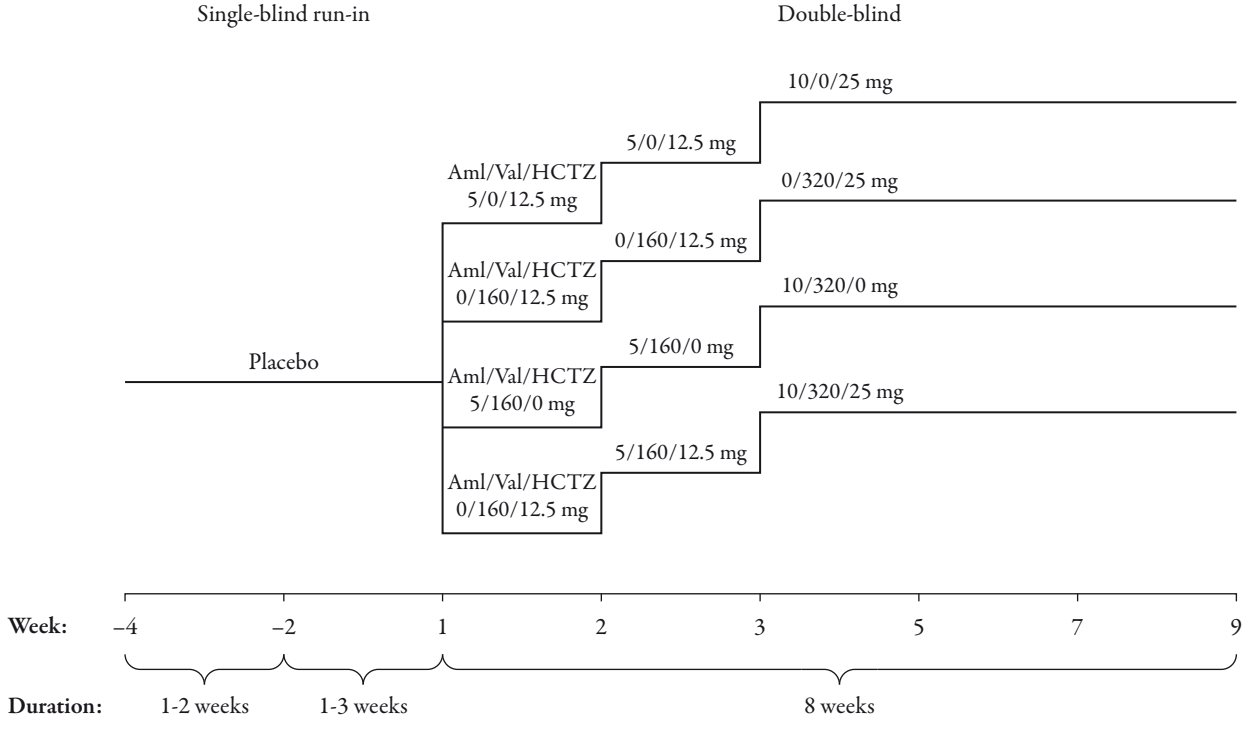
This was a multinational, randomized, double-blind trial conducted in accordance with the Declaration of Helsinki, for which the study methodology and primary results have been previously published.[18] In brief, the study population included patients aged 18-85 years

with moderate or severe hypertension, specifically with mean sitting SBP (MSSBP) of 145 to <200 mmHg and mean sitting DBP (MSDBP) of 100 to <120 mmHg. Patients may have been receiving up to three antihypertensive agents prior to entry, provided their BP did not exceed pre-specified thresholds according to the number of agents received (≥140/90 and ≥180/110 mmHg despite treatment with three or two antihypertensive agents, respectively).

The study included a withdrawal period, a placebo run-in phase, and an 8-week treatment phase, as illustrated in Figure 1.[18] Patients who had been receiving antihypertensive therapy that required gradual withdrawal proceeded to the 1-week withdrawal period. Study treatment consisted of one of the following four once-daily regimens (1:1:1:1 randomization): Aml/Val/HCTZ; Val 320 mg/HCTZ 25 mg (Val/HCTZ); Aml 10 mg/Val 320 mg (Aml/Val); or Aml 10 mg/HCTZ 25 mg (Aml/HCTZ). Patients with severe hypertension were randomized immediately, whereas all other patients first underwent a single-blind placebo run-in period for up to 4 weeks, during which patients measured SBP and DBP twice daily with a home BP monitor (HEM 705CP, Omron, IL, USA) and progressed to the double-blind treatment phase upon meeting the MSSBP and MSDBP entry criteria measured in the clinic.

During the first 2 weeks of the double-blind treatment phase, a two-stage, forced-dose titration was initiated. Patients randomized to the triple-therapy combination of Aml/Val/HCTZ received dual therapy with Val/HCTZ 160/12.5 mg for 1 week, with Aml 5 mg added for the second week (ie, half the final target triple-therapy dose). At Week 3, the full-dose combination of Aml/Val/HCTZ was initiated. For the three dual-agent regimens, each agent was given at half the final target dose for the first 2 weeks and at the final dose for the remaining

Figure 1. Study design.[18] Aml=amlodipine; HCTZ=hydrochlorothiazide; Val=valsartan.



6 weeks. No downward dose titration was permitted during the remainder of the study.

As described previously,[18] MSSBP and MSDBP were calculated based on three BP measurements taken at each clinic visit, performed after the patient had been sitting for 5 minutes and repeated at 2-minute intervals. Efficacy analyses conducted as part of the exploratory analyses reported here were based on the intent-to-treat population, ie, all randomized patients with a baseline assessment and at least one postbaseline assessment of the MSSBP and MSDBP efficacy parameters. The distribution of treatment response was summarized by the proportions and mean MSSBP of patients with MSSBP reductions of ≥60, ≥50, ≥40, ≥30, and ≥20 mmHg at Week 3 and at the end of the study. Changes in MSSBP and MSDBP from baseline to Week 3 and from baseline to endpoint in the overall study population were analyzed using an analysis of covariance (ANCOVA) model adjusted for study region and baseline BP. MSSBP changes also were analyzed by baseline MSSBP severity, with patients stratified into the following 5 categories: 145 to <150 mmHg, 150 to <160 mmHg, 160 to <170 mmHg, 170 to <180 mmHg, and ≥180 mmHg (ie, the subset of patients with severe systolic hypertension). The response rate was defined as the percentage of patients achieving an MSSBP reduction ≥20 mmHg or MSSBP <140 mmHg at study endpoint, and cumulative BP control was defined as an MSSBP/MSDBP <140/90 mmHg at any postbaseline visit. Differences in systolic response and control rates between the triple-combination dose and each dual-therapy dose were assessed at endpoint using a logistic regression model adjusted for study region.

Safety and tolerability were assessed in the safety population, ie, all patients who received at least one dose of double-blind study drug. Adverse events (AEs) related or potentially related to low BP, and discontinuations due to these AEs, were summarized in subgroups by baseline MSSBP severity.

RESULTS

Details regarding patient disposition and the baseline characteristics of the 2271 participants comprising the randomized population have been published previously.[18] Overall, the mean age was 53 years; the majority of patients were male (55%), <65 years of age (86%), and white (72%). Baseline MSSBP and MSDBP levels were 169.9 and 106.5 mmHg, respectively.

Change in MSSBP and MSDBP from Baseline to Week 3 and End of Study

In the overall study population, MSSBP and MSDBP reductions from baseline to Week 3 and to study endpoint were significantly greater for patients who received triple therapy compared with all three dual-therapy groups ($P<0.0001$ for all, except $P<0.01$ for Aml/Val MSDBP at Week 3; Figure 2). At Week 3, after receiving Val 160 mg/HCTZ 12.5 mg for 1 week followed by Aml 5 mg/Val 160 mg/HCTZ 12.5 mg for 1 week, patients had least-square mean (LSM) BP reductions of –29.6/–18.1 mmHg, resulting in a mean BP of 140.1/88.4 mmHg. This early BP reduction represented approximately 75% of the overall LSM BP reduction from baseline at study endpoint with the full dose of Aml/Val/HCTZ (–39.7/–24.7 mmHg).

A total of 646 of 2236 (29%) patients in the intent-to-treat population had severe systolic hypertension (baseline MSSBP ≥180 mmHg). The greatest LSM SBP reduction was observed for the Aml/Val/HCTZ group: 38 mmHg at Week 3 and 49.6 mmHg at end of study (Figure 3). These reductions with triple therapy were significantly greater than those for each dual therapy ($P<0.01$), except for Aml/Val at Week 3 ($P=0.11$).

Figure 2. Least-square mean reduction in (**A**) systolic and (**B**) diastolic blood pressure from baseline to Week 3 and baseline to the end of study in the overall population. Circle denotes mean postbaseline value. Hexagon denotes mean baseline value. Aml=amlodipine; HCTZ=hydrochlorothiazide; MSDBP=mean sitting diastolic blood pressure; MSSBP=mean sitting systolic blood pressure; Val=valsartan. *P<0.0001 vs. triple therapy; ‡P<0.01 vs. triple therapy

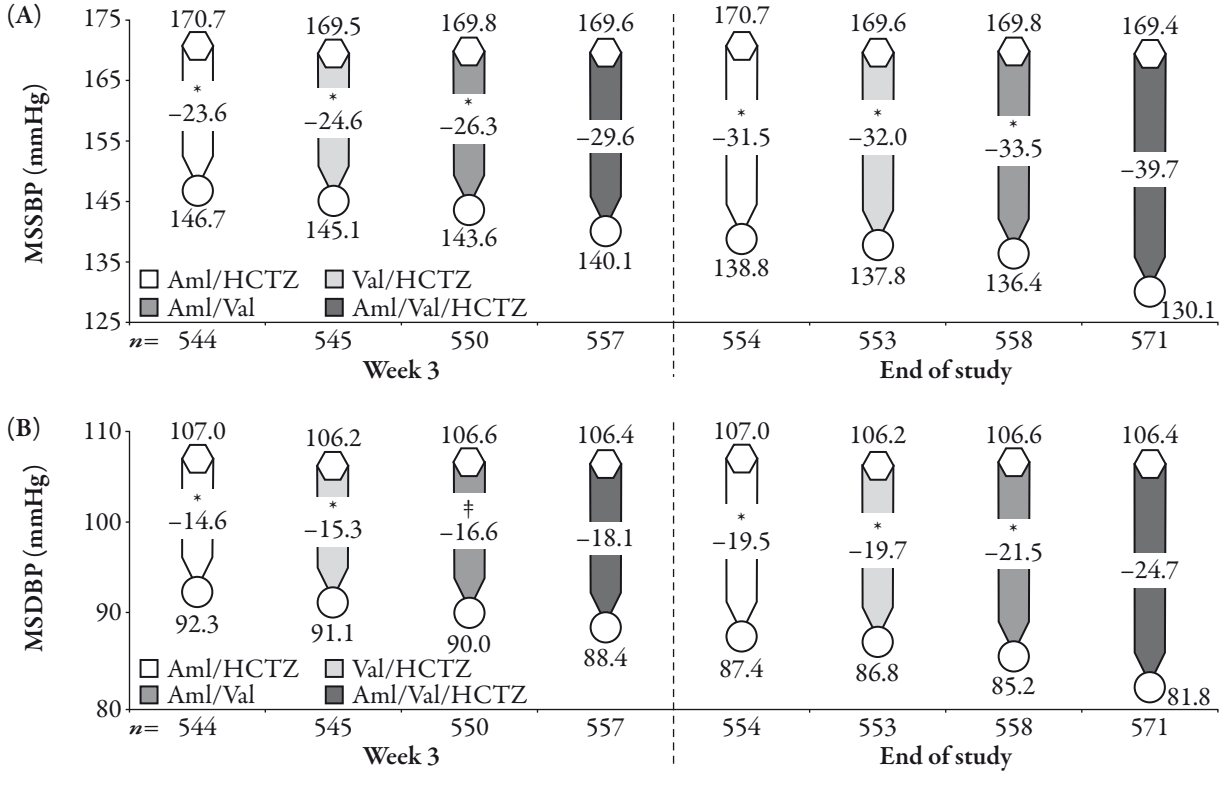
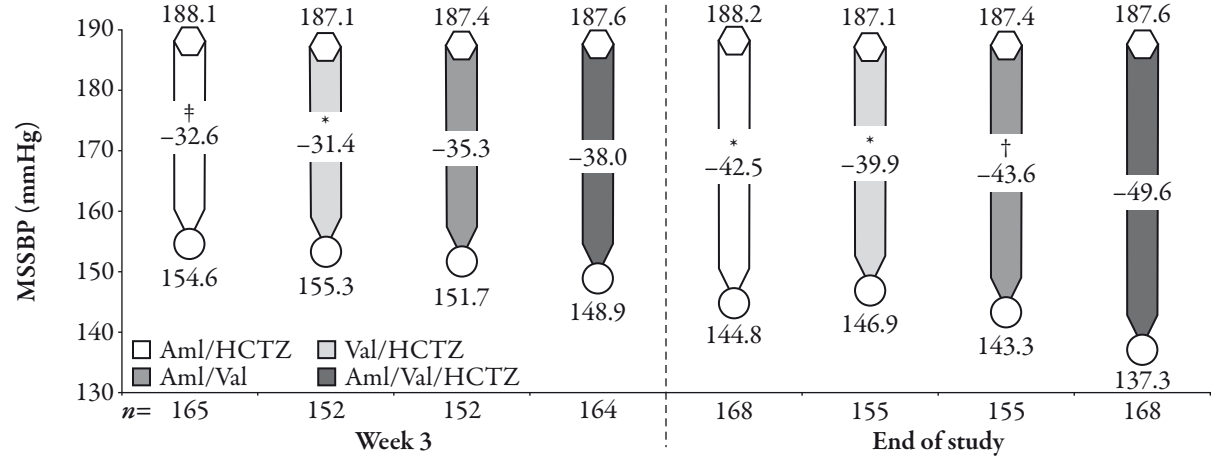


Figure 3. Least-square mean reduction in systolic blood pressure from baseline to Week 3 and end of study in the subgroup with severe systolic hypertension (baseline MSSBP ≥180 mmHg). Circle denotes mean postbaseline value. Hexagon denotes mean baseline value. Aml=amlodipine; HCTZ=hydrochlorothiazide; MSSBP=mean sitting systolic blood pressure; Val=valsartan *P<0.0001 vs. triple therapy; †P<0.001 vs. triple therapy; ‡P<0.01 vs. triple therapy.



Distribution of Treatment Response

The proportion of patients who had an MSSBP reduction ≥20 mmHg was greater with triple therapy compared with dual therapies at both Week 3 (74.5% vs. 58.8%-65.5%) and study endpoint (87.6% vs. 75.8%-81.5%; Figure 4). Similarly, more patients who received triple therapy (vs. each dual therapy) achieved MSSBP reductions of ≥30, ≥40, ≥50, and ≥60 mmHg at both Week 3 and study endpoint (Figure 4).

A comparison of the efficacy during the beginning and end of triple therapy showed that more patients had larger BP reductions at study endpoint than at Week 3 (Table 1). For example, a mean reduction of 49.6 mmHg was observed for the 129 patients in the ≥40 mmHg subgroup at Week 3, compared with a mean reduction of 52.7 mmHg for 280 patients at study endpoint. Similarly, the 14 patients in the ≥60 mmHg subgroup had achieved a 65.9 mmHg reduction at Week 3, compared with 56 patients achieving a 67.4 mmHg reduction at endpoint. Similar observations for the effect of time on treatment response were made for the dual therapies.

Change in MSSBP from Baseline to End of Study According to Baseline MSSBP Subgroup

Patients with higher baseline MSSBPs experienced greater MSSBP reductions than patients with lower baseline MSSBPs, regardless of treatment (Figure 5). Patients on triple therapy whose baseline MSSBP was 145 to <150 mmHg had an LSM reduction of 27.2 mmHg and achieved an MSSBP of 121.3 mmHg by the end of the study, whereas severely hypertensive patients (MSSBP ≥180 mmHg) had a 49.6 mmHg LSM reduction and achieved a MSSBP of 137.3 mmHg at endpoint. Changes in MSSBP were significantly greater ($P<0.05$) with triple therapy compared with each dual-therapy regimen for every baseline MSSBP subgroup, with the exception of the comparisons to Val/HCTZ and Aml/Val in the subgroup with MSSBP 150 to <160 mmHg. The benefit of triple therapy over dual therapies generally was more pronounced for patients who had higher baseline MSSBP.

Systolic Responder and Control Rates at End of Study

The percentage of patients who achieved an MSSBP reduction of ≥20 mmHg or an MSSBP <140 mmHg was significantly greater with Aml/Val/HCTZ (91.8%) compared with Aml/HCTZ (80.1%), Val/HCTZ (80.8%), or Aml/Val (85.7%; $P<0.01$ for all). Cumulative BP control at study endpoint was defined as a MSSBP/MSDBP <140/90 mmHg at any visit. Similar to BP responder rates, cumulative BP control rates were significantly higher ($P<0.0001$) with triple therapy (85.1%) than with Aml/HCTZ (64.1%), Val/HCTZ (69.6%), or Aml/Val (72.4%).

Adverse Events by Severity of Baseline Systolic Hypertension

The overall incidence of AEs was comparable across treatment groups regardless of baseline BP severity (Table 2). Dizziness occurred more frequently with triple therapy and Val/HCTZ, but the rates were similar for patients with severe and nonsevere systolic hypertension. There was a low incidence of other AEs related to, or potentially related to, low BP in all treatment groups, and the rates were similar for patients with severe and nonsevere systolic hypertension. The incidence of discontinuations due to these AEs was very low for all treatments, regardless of baseline BP severity.

Figure 4. (**A**) Distribution of treatment response at Week 3. (**B**) Distribution of treatment response at the end of study. Aml=amlodipine; HCTZ=hydrochlorothiazide; MSSBP=mean sitting systolic blood pressure; Val=valsartan.

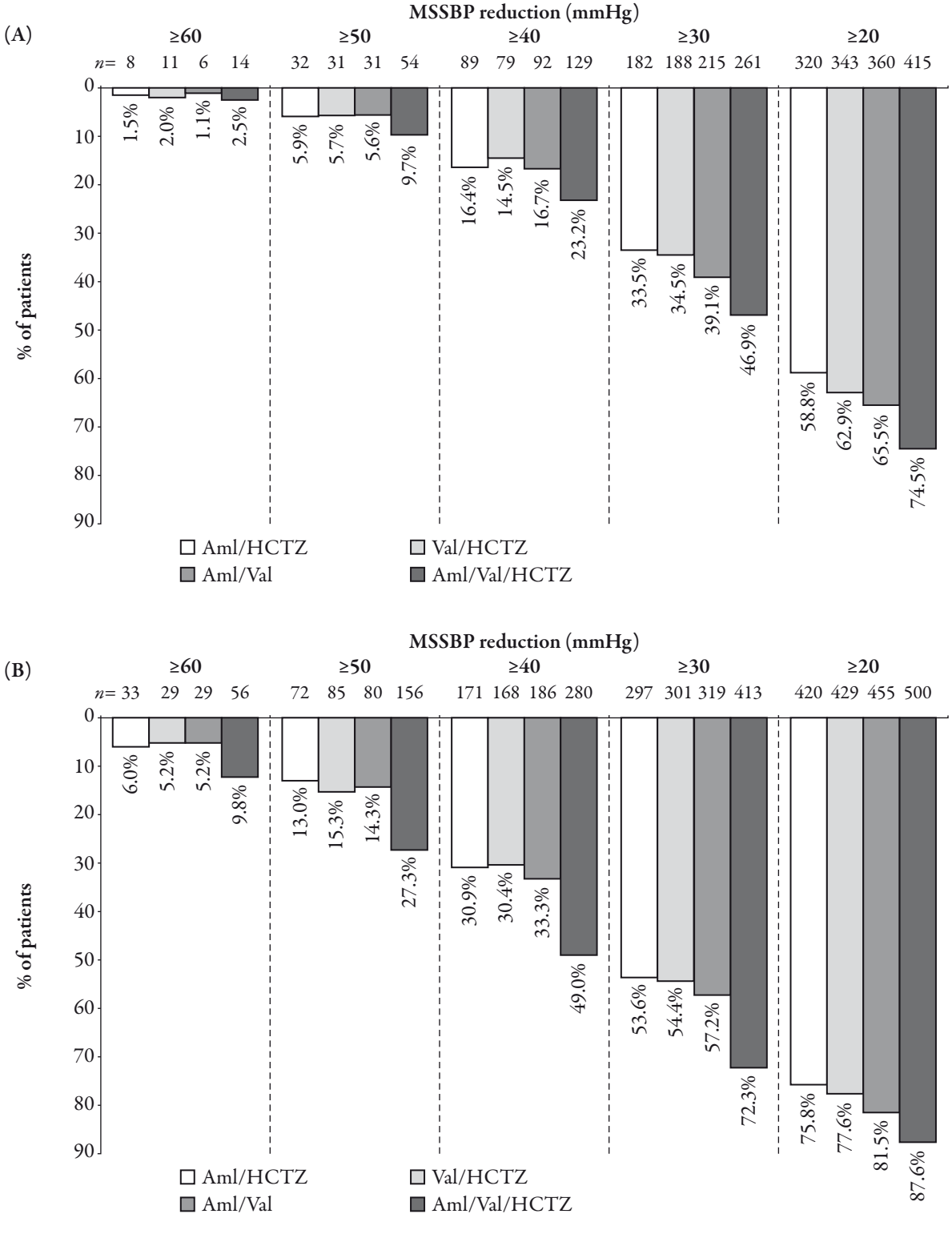


Table 1. Blood pressure reduction by category in patients receiving amlodipine/valsartan/hydrochlorothiazide (Aml/Val/HCTZ) triple therapy.

Blood pressure reduction category	Week 3	End of study
≥20 mmHg		
n	415	500
SBP reduction, mmHg	–35.6	–43.4
≥30 mmHg		
n	261	413
SBP reduction, mmHg	–41.9	–47.1
≥40 mmHg		
n	129	280
SBP reduction, mmHg	–49.6	–52.7
≥50 mmHg		
n	54	156
SBP reduction, mmHg	–57.2	–59.0
≥60 mmHg		
n	14	56
SBP reduction, mmHg	–65.9	–67.4

SBP=systolic blood pressure.

Figure 5. Least-square mean reduction in systolic blood pressure from baseline to end of study according to baseline systolic blood pressure. Aml=amlodipine; HCTZ=hydrochlorothiazide; MSSBP=mean sitting systolic blood pressure; Val=valsartan. Hexagon denotes mean baseline value; circle denotes mean postbaseline value. *P<0.0001 vs. triple therapy; †P<0.001 vs. triple therapy; ‡P<0.01 vs. triple therapy.

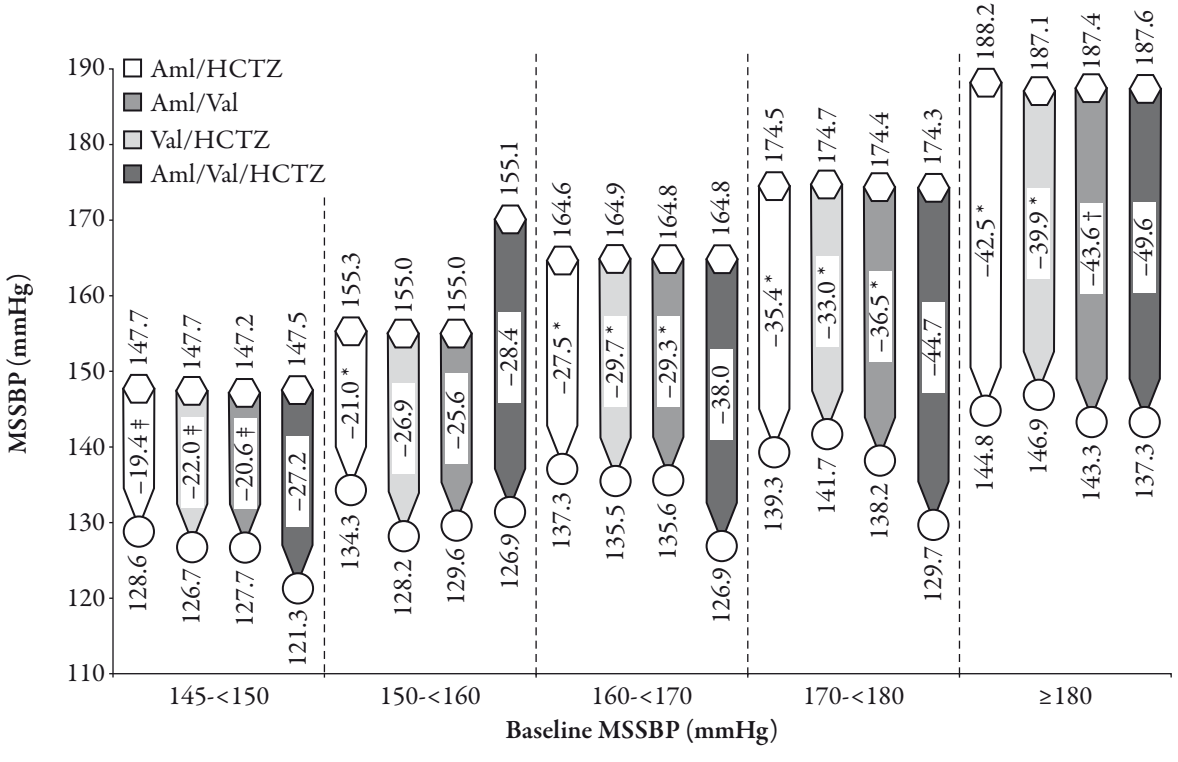


Table 2. Adverse events and discontinuations related or potentially related to low blood pressure regardless of study drug relationship (one or more patient in any treatment).

	Baseline SBP <180 mmHg				Baseline SBP ≥180 mmHg			
Adverse events	Aml/ HCTZ *n*=390	Val/ HCTZ *n*=403	Aml/ Val *n*=410	Aml/Val/ HCTZ *n*=408	Aml/ HCTZ *n*=171	Val/ HCTZ *n*=156	Aml/ Val *n*=156	Aml/Val/ HCTZ *n*=174
Any adverse event	193 (49.5)	189 (46.9)	187 (45.6)	190 (46.6)	78 (45.6)	64 (41.0)	67 (42.9)	73 (42.0)
Dizziness	14 (3.6)	28 (6.9)	10 (2.4)	30 (7.4)	8 (4.7)	11 (7.1)	3 (1.9)	15 (8.6)
Hypotension	0 (0.0)	8 (2.0)	2 (0.5)	5 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.3)
Syncope	0 (0.0)	4 (1.0)	2 (0.5)	2 (0.5)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)
Postural dizziness	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.5)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)
Orthostatic hypotension	0 (0.0)	2 (0.5)	0 (0.0)	1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Exertional dizziness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to:								
Dizziness	0 (0.0)	5 (1.2)	2 (0.5)	5 (1.2)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.6)
Hypotension	0 (0.0)	6 (1.5)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)
Syncope	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Orthostatic hypotension	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are *n* (%).
Aml=amlodipine; HCTZ=hydrochlorothiazide; SBP=systolic blood pressure; Val=valsartan.

DISCUSSION

The results of these exploratory analyses support Aml/Val/HCTZ therapy as being highly effective in lowering BP in moderate or severe hypertension. The clinically and statistically significant benefits of triple versus dual therapy were observed early, after only 1 week of Aml 5 mg/Val 160 mg/HCTZ 12.5 mg treatment, with MSSBP reaching the target therapeutic threshold of 140 mmHg and MSDBP falling below the 90 mmHg goal. The earlier BP-lowering potential of triple therapy was observed in the overall study population, as well as in the subgroup with severe systolic hypertension. More patients had greater BP reductions with triple therapy compared with dual therapy at the study endpoint and early in the course of therapy.

There has been continual discussion not only of target BP levels for hypertensive patients at various cardiovascular risks, but also of the definition of "efficacy" as it applies to antihypertensive regimens.[19] Although changes in BP levels from baseline are paramount from a regulatory standpoint, clinical practice guidelines focus primarily on specific BP thresholds (ie, <140/90 mmHg for the general hypertensive population and <130/80 mmHg for patients with diabetes or chronic kidney disease).[1] It is well accepted that the likelihood of rapidly achieving a specific BP on a new antihypertensive regimen is impacted by the individual patient's pretreatment BP level. Reducing SBP is regarded as more critical and challenging than reducing DBP.[1,20] Two important factors associated with difficulty controlling SBP are the presence of diabetes and the severity of baseline SBP.[21] In this regard, the findings of early SBP reduction among Aml/Val/HCTZ-treated patients with severe systolic hypertension (SBP ≥180 mmHg) are relevant.

Of potential clinical importance is the fact that greater MSSBP reductions were observed

in patients with greater baseline MSSBP levels with triple therapy as well as the dual therapies. Importantly, the overall incidence of AEs related or potentially related to low BP, such as dizziness, hypotension, orthostatic hypotension, or syncope, was not affected by baseline MSSBP severity. Thus, despite the inherent shortcomings of subgroup and post-hoc analyses, these efficacy and safety findings lend support for using more intensive treatment strategies for patients with more severe hypertension.

Clinical practice guidelines for treating hypertensive patients provide guidance regarding target BP levels,[1,15,22] but do not specify a target timeframe for achieving such goals. The present analyses support the ability of triple combination therapy to promptly reduce BP. Although limited, accumulating data derived from clinical trials of antihypertensive regimens suggest a positive impact of prompt BP control on cardiovascular and cerebrovascular outcomes, with a series of studies supporting efforts to achieve BP goals within 6 months of initiating antihypertensive therapy.[23,24] In addition, data from the Valsartan Antihypertensive Long-term Use Evaluation (VALUE), the Anglo-Scandinavian Cardiac Outcomes-Blood Pressure Lowering Arm (ASCOT-BPLA), and the Study on Cognition and Prognosis in the Elderly (SCOPE) suggest that even earlier BP control, within a 1-3 month timeframe, attenuates the rates of certain vascular events.[24-27] In VALUE, patients who were either (1) previously untreated with a ≥10 mmHg SBP reduction within the first month or (2) previously treated with no SBP increase upon switching to Aml or Val-based study treatment were categorized as being "immediate responders."[24] In this subset, the risks of combined cardiac events, stroke, and all-cause mortality were reduced significantly, by 12% ($P<0.01$), 17% ($P<0.05$), and 10% ($P<0.05$), respectively, in comparison to "nonimmediate responders."[24] ASCOT-BPLA and SCOPE both demonstrated between-group differences in BP control 3 months after treatment initiation, which may have contributed to between-group differences in certain secondary outcomes.[25-27] Further research is needed to elucidate the degree to which the lag time from treatment initiation to target BP attainment impacts vascular outcomes and mortality. Nonetheless, the ability to achieve early BP control within weeks is a favorable antihypertensive attribute and one that appears to apply to Aml/Val/HCTZ.

In conclusion, the triple combination of Aml/Val/HCTZ was more efficacious than any of its component dual therapies in reducing BP. Triple therapy also produced higher clinical response rates. These beneficial effects of Aml/Val/HCTZ were observed early in the course of therapy. In addition, reductions in BP were proportionate to the severity of hypertension, further supporting the clinical utility of triple combination therapy.

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