Original Paper

Efficacy of the Combination of Amlodipine and Valsartan in Patients With Hypertension Uncontrolled With Previous Monotherapy: The Exforge in Failure After Single Therapy (EX-FAST) Study

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In this randomized, double-blind, multicenter study, patients whose blood pressure (BP) was uncontrolled by monotherapy were switched directly to amlodipine/valsartan 5/160 mg (n=443) or 10/160 mg (n=451). After 16 weeks, BP control (levels <140/90 mm Hg or <130/80 mm Hg for diabetics) was achieved in 72.7% (95% confidence interval [CI], 68.6–76.9) of patients receiving amlodipine/valsartan 5/160 mg and in 74.8% (95% CI, 70.8–78.9) receiving amlodipine/valsartan 10/160 mg. Incremental reductions from baseline in mean sitting systolic and diastolic BP were significantly greater with the higher dose (20.0±0.7 vs 17.5±0.7 mm Hg; P=.0003 and 11.6±0.4 vs 10.4±0.4 mm Hg;

P=.0046). Incremental BP reductions were also achieved with both regimens irrespective of previous monotherapy, hypertension severity, diabetic status, body mass index, and age. Peripheral edema was the most frequent adverse event. These results provide support for the BP-lowering benefits of complementary antihypertensive therapy with amlodipine and valsartan in patients with hypertension uncontrolled by previous monotherapy. J Clin Hypertens (Greenwich). 2008;10:185–194. ©2008 Le Jacq

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Worldwide hypertension control remains suboptimal despite the availability of a range of effective antihypertensive medications.[1–5] A majority of patients with hypertension, especially those at high risk, require ≥2 agents for blood pressure (BP) control to be achieved.[6,7] In these individuals, multiple medications may be administered separately or in fixed-dose combinations, the latter reducing treatment complexity and potentially leading to improved compliance.[8–10]

Treatment guidelines note that the combination of an angiotensin receptor blocker (ARB) and a calcium channel blocker (CCB), similar to the combination of an angiotensin-converting enzyme inhibitor (ACEI) or an ARB plus a diuretic, provides an effective option for patients with hypertension.[7] ACEI/CCB and ARB/CCB combinations incorporate monotherapy components that act via complementary mechanisms of action[11,12] and

therefore achieve greater sustained BP reductions than when the respective monocomponents are administered alone.[13–15] Tolerability benefits may also be gained from rational drug combinations, such as edema reduction when an ACEI or an ARB is added to a CCB.[16,17]

This study was designed to evaluate improvement in BP control after switching to one of two doses of a CCB/ARB combination (amlodipine/valsartan) in patients with hypertension not controlled with prior monotherapy.

PATIENTS AND METHODS
Study Design and Patients
This was a randomized, double-blind, multinational, parallel-group study conducted at 132 centers in 8 countries (France, Spain, Belgium, Norway, Switzerland, Slovakia, Canada, and the United States). Patients were screened at visit 1 (week –2 to –1) to assess eligibility for participation in the study. At visit 2 (day 1), patients discontinued their previous antihypertensive regimens and without washout were randomized in a 1:1 ratio to 16 weeks' treatment with either amlodipine/valsartan 5/160 mg or amlodipine/valsartan 10/160 mg. If BP was uncontrolled at visit 4 (week 8) (ie, BP was ≥140/90 mm Hg in nondiabetics or ≥130/80 mm Hg in diabetics), open-label hydrochlorothiazide (HCTZ) 12.5 mg was added. No HCTZ was added if BP was controlled. If BP remained uncontrolled at visit 5 (week 12), the HCTZ dose was increased to 25 mg (patients with controlled BP at visit 4 but not at visit 5 received HCTZ 12.5 mg). All study medications were administered in the morning.

Male and female adult outpatients were eligible for inclusion in the treatment phase of the study if they had uncontrolled hypertension at both screening and randomization despite current antihypertensive monotherapy (defined as treatment with a single antihypertensive agent). All patients were required to be treated with monotherapy for a minimum of 2 months before screening. Patients were excluded if they had a systolic BP (SBP) level ≥180 mm Hg (≥160 mm Hg in diabetics) or a diastolic BP (DBP) level ≥110 mm Hg (≥100 mm Hg in diabetics) at any time between screening and randomization. Enrollment of patients with type 1 diabetes or poorly controlled type 2 diabetes (glycosylated hemoglobin >8.0%) was not permitted. Patients were also excluded if they had evidence of hepatic disease (alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal at visit 1 or history of hepatic encephalopathy, esophageal varices, or portocaval

shunt) or renal impairment (serum creatinine >1.5 times the upper limit of normal at visit 1 or history of dialysis or nephrotic syndrome). Other exclusion criteria included evidence of secondary hypertension; history of cerebrovascular accident, myocardial infarction, or New York Heart Association grade II to IV heart failure; transient ischemic attack or percutaneous coronary intervention or coronary artery bypass graft surgery 12 months before screening; second- or third-degree heart block without a pacemaker; concomitant unstable angina pectoris or potentially life-threatening arrhythmia or symptomatic arrhythmia; or clinically significant valvular heart disease. Women who were pregnant, nursing, or of childbearing potential and not using acceptable contraception were also excluded. After randomization, patients were not permitted to use any antihypertensive drugs other than study medication or to take any chronic treatment that may have interfered with BP control. The study was performed with institutional review board/independent ethics committee/research ethics board approval and was conducted in accordance with the International Conference on Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice (with applicable local regulations) and the Declaration of Helsinki. All patients gave written informed consent.

BP Measurement
Sitting and standing BP values were measured using a standard calibrated mercury or aneroid sphygmomanometer. At screening, BP was measured in both arms, and the arm with the higher reading was used for all subsequent BP measurements. Three consecutive sitting SBP/DBP measurements were taken at 1- to 2-minute intervals at each study visit (day 1 and weeks 4, 8, 12, and 16). The mean of these measurements was used as the average sitting office BP. A single measure of standing SBP/DBP was also recorded within 2 minutes after the last sitting BP measurement. All readings were taken at drug trough (ie, before taking the morning dose of medication).

Efficacy Variables
The primary efficacy variable was the proportion of patients in whom BP control was achieved at the study end point (week 16). BP control was defined as mean sitting BP <140/90 mm Hg in nondiabetic patients and <130/80 mm Hg in diabetic patients. The study end point (week 16) was defined as the week 16 value or the last nonmissing postbaseline value (last observation carried forward [LOCF]).

Table I. Baseline Demographic and Clinical Characteristics in the Randomized Population

	Amlodipine/Valsartan 5/160 mg (N=443)	Amlodipine/Valsartan 10/160 mg (N=451)	Total Study Population (N=894)
Age, y[a]	58.5±12.3	58.6±12.0	58.5±12.2
Age category			
<65 y	309 (69.8)	311 (69.0)	620 (69.4)
≥65 y	134 (30.2)	140 (31.0)	274 (30.6)
≥70 y	93 (21.0)	91 (20.2)	184 (20.6)
≥75 y	53 (12.0)	40 (8.9)	93 (10.4)
Sex			
Male	232 (52.4)	211 (46.8)	443 (49.6)
Female	211 (47.6)	240 (53.2)	451 (50.4)
Race			
White	405 (91.4)	418 (92.7)	832 (92.1)
Black	19 (4.3)	17 (3.8)	36 (4.0)
Other	19 (4.3)	16 (3.5)	35 (3.9)
MSSBP, mm Hg[a]	149.8±9.7	150.4±10.5	150.1±10.1
MSDBP, mm Hg[a]	90.8±7.7	90.6±7.6	90.7±7.7
Sitting pulse, bpm[a]	71.2±9.3	71.6±9.7	71.4±9.5
Prior treatment			
ARB	176 (39.7)	176 (39.0)	352 (39.4)
ACEI	92 (20.8)	106 (23.5)	198 (22.1)
β-Blocker	77 (17.4)	55 (12.2)	132 (14.8)
CCB	54 (12.2)	70 (15.5)	124 (13.9)
Diuretic	41 (9.3)	39 (8.6)	80 (8.9)
Other	3 (0.7)	5 (1.1)	8 (0.9)
Severity of hypertension[b]			
More severe	97 (22.8)	101 (22.9)	198 (22.8)
Less severe	329 (77.2)	341 (77.1)	670 (77.2)
Diabetic status			
Diabetic	72 (16.3)	74 (16.4)	146 (16.3)
Nondiabetic	371 (83.7)	377 (83.6)	748 (83.7)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; bpm, beats per minute; CCB, calcium channel blocker; MSDBP, mean sitting diastolic blood pressure; MSSBP, mean sitting systolic blood pressure. Values are No. (%) unless otherwise indicated. [a]Mean ± SD. [b]More severe, ≥160 and <180 mm Hg/≥100 and <110 mm Hg; less severe, ≥140 and <160 mm Hg/≥90 and <100 mm Hg. Blood pressure at baseline is with monotherapy (ie, before switch to amlodipine/valsartan therapy).

The main secondary efficacy variable was the proportion of patients in whom BP control was reached before the addition of HCTZ (ie, at the pre-HCTZ end point [week 8], defined as the week 8 value or the LOCF at week 8). Other secondary efficacy variables included overall BP control rates at all weeks and DBP control rates (<90 mm Hg in nondiabetic patients and <80 mm Hg in patients with diabetes) as well as the change from baseline in mean sitting SBP and DBP (MSSBP and MSDBP, respectively) at all weeks/end points.

Prospectively planned analyses were also conducted to evaluate BP control rates and changes from baseline BP in patient subgroups divided according to class of prior antihypertensive therapy; age group;

diabetic status; severity of hypertension (defined by 2 categories according to BP levels with monotherapy before switch: "more severe" if baseline mean sitting BP ≥160 and <180 mm Hg/≥100 and <110 mm Hg; "less severe" if baseline mean sitting BP ≥140 and <160 mm Hg/≥90 and <100 mm Hg); body mass index (BMI); and race. Safety and tolerability were assessed by monitoring and recording all adverse events, serious adverse events, laboratory safety evaluation results, physical examination findings, electrocardiographic data, and vital signs.

Statistical Analysis
A sample size of 926 patients, randomized in a 1:1 ratio, was required to ensure that the study had
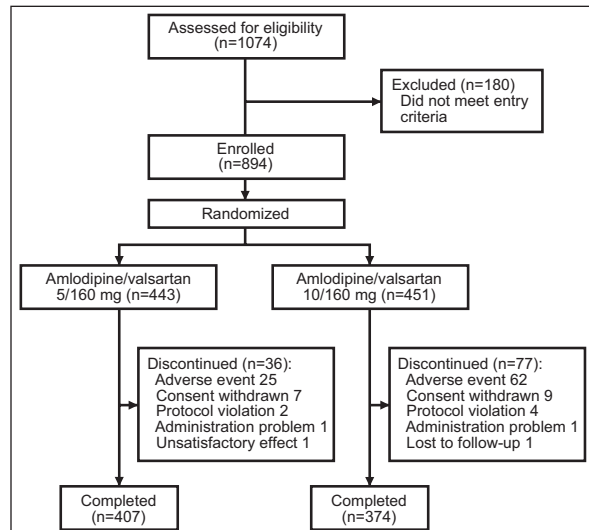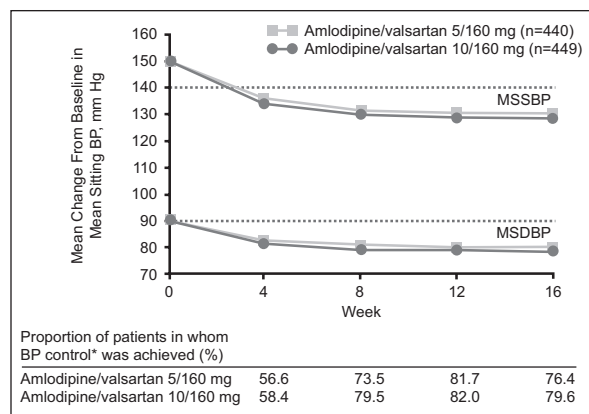
Figure 1. Patient disposition.

Figure 2. Incremental antihypertensive effects following a direct switch to amlodipine/valsartan 5/160 mg and 10/160 mg in patients with hypertension previously uncontrolled with monotherapy. Mean change from baseline in mean sitting systolic and diastolic blood pressure (MSSBP and MSDBP, respectively) and the proportion of patients in whom blood pressure (BP) control* was achieved over time (intent-to-treat population).*BP control is defined as BP <140/90 mm Hg for nondiabetic patients and <130/80 mm Hg for diabetic patients.

90% power to detect a between–treatment group difference in the main secondary efficacy variable using a 2-sided 5% significance level. For this calculation, it was assumed that BP control rates at the pre-HCTZ end point (week 8) would be 46.0% in patients receiving amlodipine/valsartan 5/160 mg and 56.6% in those receiving amlodipine/valsartan 10/160 mg, corresponding to an odds ratio of 1.533.

Efficacy analyses were conducted for the intent-to-treat population, which consisted of all randomized patients with a baseline and at least 1 post-baseline efficacy assessment. The safety population consisted of all patients who had received at least 1 dose of double-blind study medication.

For the primary efficacy outcome (ie, the proportion of patients in whom BP control was achieved at the study end point [week 16]), unadjusted control rates and corresponding asymptotic 2-sided 95% confidence intervals (CIs) were calculated for each treatment group. The proportion of patients with controlled BP at end point weeks 16 and week 8 and at weeks 4, 8, 12, and 16 (LOCF not applied) were compared using a logistic regression model with treatment strategy and diabetic status as factors and baseline MSSBP and MSDBP as covariates. The odds of having controlled BP, with corresponding 2-sided 95% CIs, were also assessed.

Changes from baseline in MSSBP and MSDBP at weeks 4, 8, 12, and 16 were analyzed using analysis of covariance (ANCOVA) with treatment strategy, country, and diabetic status as factors and baseline MSSBP or MSDBP, respectively, as a covariate. Differences between the least squares means and associated 95% CIs were calculated. For the proportion of patients in whom DBP control was achieved, unadjusted control rates and corresponding asymptotic 2-sided 95% CIs were calculated. For the subgroup analyses, descriptive statistics for changes in MSSBP and MSDBP and unadjusted BP control rates with asymptomatic 2-sided 95% CIs were determined.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 894 patients were enrolled and randomized to treatment with amlodipine/valsartan 5/160 mg (n=443) or amlodipine/valsartan 10/160 mg (n=451) (Figure 1). Baseline demographics and clinical characteristics were well balanced between the 2 treatment groups (Table I). The study was completed by 781 patients: 407/443 (91.9%) received the lower dose (5/160 mg) and 374/451 (82.9%) received the higher dose (10/160 mg). Among patients treated with amlodipine/valsartan 5/160 mg, 24.8% received additional treatment with HCTZ 12.5 mg (n=94 at week 8; n=16 at week 12), of whom 11.5% required HCTZ 25 mg at week 12. For patients given amlodipine/valsartan 10/160 mg, 19.1% required HCTZ 12.5 mg (n=65 at week 8; n=21 at week 12), 6.4% of whom received HCTZ 25 mg at week 12.

Primary and Secondary Efficacy Outcomes

At the study end point (week 16), the primary outcome of BP control was achieved in 320 patients (72.7%; 95% CI, 68.6–76.9) in the amlodipine/

Table II. Incremental Blood Pressure–Lowering Effects of Amlodipine/Valsartan 5/160 mg and 10/160 mg in the Intent-to-Treat Population and According to the Severity of Hypertension at Baseline

Week and Disease Severity	Amlodipine/Valsartan 5/160 mg MSSBP/MSDBP			Amlodipine/Valsartan 10/160 mg MSSBP/MSDBP			Amlodipine/Valsartan 5/160 vs 10/160 mg MSSBP/MSDBP	
	No.[a]	Baseline, mm Hg	Change From Baseline, mm Hg (SEM)	No.[a]	Baseline, mm Hg	Change From Baseline, mm Hg (SEM)	Difference in Change (95% CI)	P Value
Week 4								
Intent-to-treat[b]	440	149.8/90.8	−13.9 (0.7)/−8.4 (0.4)	449	150.4/90.6	−16.1 (0.7)/−9.7 (0.4)	2.2 (0.8–3.5)/1.3 (0.4–2.2)	.0016/.0038
Less severe[c]	329	147.3/89.8	−13.1/−8.2	341	147.1/89.3	−15.0/−9.3		
More severe[d]	97	160.7/95.9	−20.7/−10.9	101	162.7/95.5	−23.6/−12.0		
Week 8								
Intent-to-treat[b]	423	149.6/90.9	−18.0 (0.7)/−9.9 (0.5)	410	150.8/90.9	−20.8 (0.7)/−11.9 (0.5)	2.8 (1.4–4.1)/2.0 (1.1–2.9)	<.0001/<.0001
Less severe[c]	319	147.2/89.8	−16.1/−9.3	310	147.4/89.7	−18.5/−11.2		
More severe[d]	91	160.3/96.0	−24.8/−13.2	93	163.4/95.7	−29.7/−15.1		
End point week 8[e]								
Intent-to-treat[b]	440	149.8/90.8	−16.5 (0.7)/−9.3 (0.5)	449	150.4/90.6	−19.2 (0.7)/−11.3 (0.5)	2.7 (1.3–4.1)/2.1 (1.2–3.0)	.0001/<.0001
Less severe[c]	329	147.3/89.8	−15.5/−9.0	341	147.1/89.3	−17.5/−10.8		
More severe[d]	97	160.7/95.9	−23.9/−12.5	101	162.7/95.5	−28.8/−14.7		
Week 12								
Intent-to-treat[b]	410	149.9/91.0	−19.2 (0.6)/−10.8 (0.4)	388	150.7/91.0	−21.8 (0.6)/−12.2 (0.4)	2.6 (1.4–3.9)/1.4 (0.5–2.2)	<.0001/.0016
Less severe[c]	309	147.3/89.8	−17.5/−10.8	296	147.4/89.7	−19.7/−12.1		
More severe[d]	91	160.3/96.0	−25.9/−14.1	87	163.1/95.5	−31.0/−15.4		
Week 16								
Intent-to-treat[b]	406	149.9/90.9	−19.4 (0.7)/−11.3 (0.4)	378	150.7/91.0	−22.1 (0.7)/−12.4 (0.4)	2.7 (1.4–4.0)/1.1 (0.2–1.9)	<.0001/.0121
Less severe[c]	307	147.4/89.8	−17.3/−10.9	289	147.3/89.7	−19.9/−12.3		
More severe[d]	89	160.4/95.9	−25.8/−14.6	85	163.1/95.9	−30.6/−14.8		
Endpoint Week 16[f]								
Intent-to-treat[b]	440	149.8/90.8	−17.5 (0.7)/−10.4 (0.4)	449	150.4/90.6	−20.0 (0.7)/−11.6 (0.4)	2.5 (1.1–3.8)/1.2 (0.4–2.1)	.0003/.0046
Less severe[c]	329	147.3/89.8	−16.3/−10.5	341	147.1/89.3	−18.3/−11.7		
More severe[d]	97	160.7/95.9	−24.7/−13.9	101	162.7/95.5	−29.7/−14.5		

Abbreviations: CI, confidence interval; MSDBP; mean sitting diastolic blood pressure; MSSBP; mean sitting systolic blood pressure; SEM, standard error of the mean. [a]Number of patients with nonmissing measurements at respective week. [b]The least squares mean change from baseline is shown at each week for the intent-to-treat population. [c]Patients with MSSBP at baseline of ≥140 and <160 mm Hg or MSDBP of ≥90 and <100 mm Hg. [d]Patients with MSSBP at baseline of ≥160 and <180 mm Hg or MSDBP of ≥100 and <110 mm Hg. [e]Pre-hydrochlorothiazide end point (ie, week 8 or last observation carried forward [LOCF] value. [f]End point week 16 is the value at week 16 or LOCF value. The intent-to-treat population is based on a cutoff of 140/90 mm Hg; diabetic patients with a blood pressure value of 130–140 and 80–90 mm Hg were not included in the severity subgroup population.
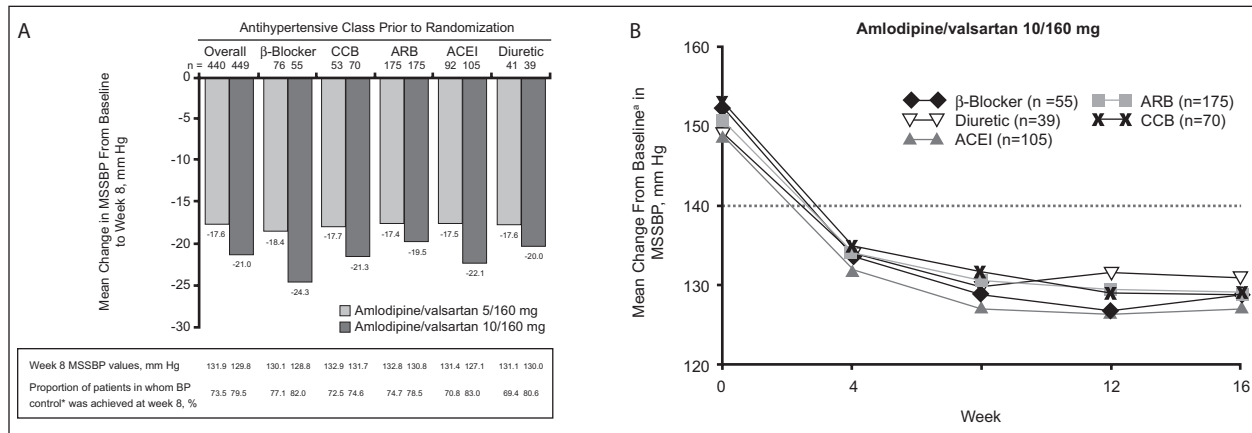
Figure 3. The impact of prior antihypertensive monotherapy in patients switched directly to amlodipine/valsartan on mean change in mean sitting systolic blood pressure (MSSBP) from baseline to week 8 and the proportion of patients in whom blood pressure (BP) control* is achieved at week 8 (A) and mean change from baseline in MSSBP over time with amlodipine/valsartan 10/160 mg according to previous antihypertensive monotherapy (B). *BP control is defined as BP <140/90 mm Hg for nondiabetic patients and BP <130/80 mm Hg for diabetic patients. CCB indicates calcium channel blocker; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor. [a]Baseline MSSBP values (mm Hg): β-blocker, 152.3; ARB, 150.3; ACEI, 148.8; diuretic, 149.2; and CCB, 152.7.

valsartan 5/160 mg (± HCTZ) group and 336 (74.8%; 95% CI, 70.8–78.9) treated with amlodipine/valsartan 10/160 mg (± HCTZ). The corresponding estimated odds for BP control were 1.35 (95% CI, 1.04–1.75) and 1.64 (95% CI, 1.27–2.13), respectively, giving an odds ratio of 0.82 (95% CI, 0.59–1.14). At the pre-HCTZ end point (week 8), the proportion of patients in whom BP control was achieved was greater with the higher dose compared with the lower dose (76.4% vs 71.1%; P<.03 [logistic regression]). DBP control at the study end point (week 16) was achieved in 85.7% of patients in the amlodipine/valsartan 5/160 mg treatment group (95% CI, 82.4–88.9) and in 87.3% of those treated with amlodipine/valsartan 10/160 mg (95% CI, 84.2–90.4). Figure 2 shows the change from baseline in MSSBP and MSDBP over time for both treatments. At the study end point (week 16), incremental reductions from baseline in mean sitting BP were significantly greater in patients receiving the higher dose than in those treated with amlodipine/valsartan 5/160 mg (MSSBP, 20.0±0.7 mm Hg vs 17.5±0.7 mm Hg, respectively [P=.0003, ANCOVA]; MSDBP, 11.6±0.4 mm Hg vs 10.4±0.4 mm Hg [P=.0046, ANCOVA]; Table II).

Subgroup Evaluations

Prior Antihypertensive Therapy. BP control rates in the individual treatment groups did not differ over time by previous antihypertensive monotherapies. The proportion of patients in whom BP control was reached at week 8 ranged from 66.7% to 77.1% (range includes "other" prior monotherapy) for amlodipine/valsartan 5/160 mg and 74.6% to 83.0%

for amlodipine/valsartan 10/160 mg (Figure 3A). The 2 treatment groups were also similar with respect to the change from baseline in mean sitting BP across all prior medications, and by week 4 MSSBP was <140 mm Hg for all previous monotherapy groups (Figure 3B). Incremental MSSBP reductions at week 8 were in the range of 17.4 to 18.7 mm Hg (which includes "other" prior monotherapy) in the amlodipine/valsartan 5/160 mg group and 19.5 to 24.3 mm Hg for the 10/160 mg treatment arm (Figure 3A). In those patients who had previously received amlodipine 10 mg monotherapy, changes in MSSBP at week 8 were –9.6 mm Hg and –16.3 mm Hg, respectively, with amlodipine/valsartan 5/160 mg and 10/160 mg. The corresponding changes in those previously treated with valsartan 160 mg monotherapy were –14.9 mm Hg and –18.5 mm Hg.

Severity of Hypertension. At baseline, 198 patients had more severe hypertension (Table I). In both treatment groups, changes in mean sitting BP were numerically greater the more severe the hypertension. The change from baseline in MSSBP according to severity of hypertension is shown in Figure 4 for amlodipine/valsartan 10/160 mg. The incremental MSSBP reductions in the more severe hypertension subgroup were –23.9 mm Hg for the lower dose and –28.8 mm Hg for the higher dose at the pre-HCTZ end point week 8 and –24.7 mm Hg and –29.7 mm Hg, respectively, at study end point week 16 (Table II).

Diabetic Status. Among patients with diabetes (n=145), control of BP to values <140/90 mm Hg at weeks 8 and 16 were comparable to the rates of BP

Table III. Most Frequent Adverse Events by Treatment Group

	Amlodipine/Valsartan 5/160 mg (N=443)	Amlodipine/Valsartan 10/160 mg (N=450)
Patients		
Reported an adverse event	187 (42.2)	253 (56.2)
Reported a treatment-related adverse event	60 (13.5)	140 (31.1)
Reported a serious adverse event	3 (0.7)	13 (2.9)
Adverse event		
Peripheral edema	36 (8.1)	113 (25.1)
Headache	10 (2.3)	17 (3.8)
Back pain	10 (2.3)	15 (3.3)
Dizziness	9 (2.0)	10 (2.2)
Muscle spasms	7 (1.6)	9 (2.0)
Treatment-related adverse event		
Peripheral edema	30 (6.8)	100 (22.2)
Headache	0 (0.0)	10 (2.2)
Dizziness	0 (0.0)	9 (2.0)

Values are No. (%). Adverse events at 16 weeks were considered frequent if they occurred in ≥2% of the safety population for any regimen.

control observed in nondiabetic patients (Figure 5). In the amlodipine/valsartan 5/160 mg treatment arm, BP control at week 16 was achieved in 48 of 61 diabetic patients (78.7%; 95% CI, 68.4–89.0), while in the amlodipine/valsartan 10/160 mg group a BP level of <140/90 mm Hg was achieved in 54 of 59 patients with diabetes (91.5%; 95% CI, 84.4–98.6). The respective values at week 8 were 69.7% and 80.0%. The proportions of diabetic patients in whom the lower BP target of <130/80 mm Hg was reached at week 16 were 45.9% and 40.7% for the lower and higher doses, respectively. Reductions in MSSBP/MSDBP from baseline to week 16 in the diabetic subgroup were similar for the 2 regimens: 16.8/9.5 mm Hg for amlodipine/valsartan 5/160 mg and 17.7/11.5 mm Hg for amlodipine/valsartan 10/160 mg.

Age. At the study end point (week 16), BP control rates for the low and high dose amlodipine/valsartan groups were 73.4% and 78.6%, respectively, for patients younger than 65 years, compared with 71.2% and 66.4%, respectively, for patients aged 65 years or older. Within the 2 groups, mean incremental reductions in MSSBP did not differ greatly with respect to age, although minor differences were seen for MSDBP. In the amlodipine/valsartan 5/160 mg arm, the mean change in mean sitting BP at the end point (week 16) was –17.9/–11.6 mm Hg in patients younger than 65 years and –18.2/–9.8 mm Hg in patients 65 years or older. The corresponding reductions in MSSBP/MSDBP with amlodipine/valsartan 10/160 mg were 20.6/12.6 and 21.2/11.3 mm Hg, respectively.
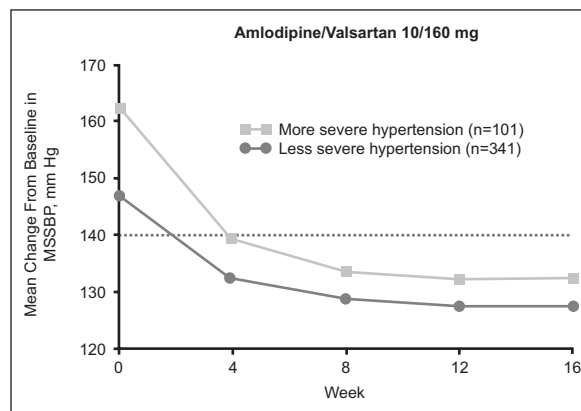

Figure 4. Incremental antihypertensive effects following a direct switch to amlodipine/valsartan 5/160 mg and 10/160 mg in patients with hypertension previously uncontrolled with monotherapy. Mean change from baseline in mean sitting systolic blood pressure (MSSBP) over time with amlodipine/valsartan 10/160 mg according to severity of hypertension (less severe hypertension defined as a baseline blood pressure [BP] value of ≥140 and <160 mm Hg/≥90 and <100 mm Hg; more severe hypertension defined as a baseline BP value of ≥160 and <180 mm Hg/≥100 and <110 mm Hg).

BMI, Sex, and Race. In the subgroup of patients with a BMI ≥30 kg/m², BP control at the study end point (week 16) was achieved in 115 of 180 (63.9%) patients receiving the lower dose of the combination and by 118 of 170 (69.4%) patients treated with the higher dose. Corresponding reductions in mean sitting BP were 17.2/10.8 mm Hg and 18.6/11.2 mm Hg, respectively. There were no major differences between treatment groups with respect to sex or race.
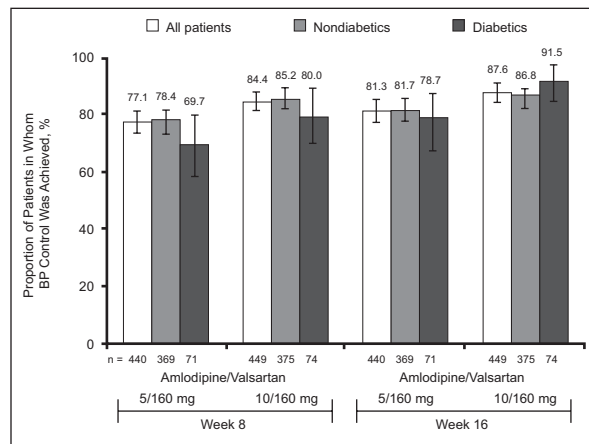
Figure 5. Proportion of diabetic and nondiabetic patients in whom a blood pressure (BP) goal of <140/90 mm Hg was reached with amlodipine/valsartan 5/160 and 10/160 mg at week 8 and week 16 (error bars show 95% confidence intervals).

Safety and Tolerability

There were no deaths during the study. Overall, 113 patients discontinued therapy: 36 of 443 patients (8.1%) in the amlodipine/valsartan 5/160 mg group and 77 of 451 (17.1%) in the amlodipine/valsartan 10/160 mg arm. The most common reasons for discontinuation were adverse events, involving 25 patients (5.6%) receiving the lower dose and 62 (13.7%) treated with the higher dose (Figure 1). Adverse events were not severe; the most frequent were peripheral edema, headache, back pain, dizziness, and muscle spasms (Table III). Peripheral edema was the most frequent drug-related adverse event and led to discontinuation in 10 patients (2.3%) in the amlodipine/valsartan 5/160 mg group and in 41 patients (9.1%) treated with amlodipine/valsartan 10/160 mg. The majority of reported cases of peripheral edema occurred between the time of randomization and week 8 (5.6% with amlodipine/valsartan 5/160 mg and 20.4% with amlodipine/valsartan 10/160 mg; *P*<.0001). Serious adverse events occurred in 3 patients (0.7%) receiving the lower dose and 13 (2.9%) patients in the other group. Only 1 serious adverse event, a case of nephrotic syndrome in 1 patient (0.2%) in the amlodipine/valsartan 5/160 mg group, was considered drug-related by the treating physician. Orthostatic BP changes (ie, decreases of at least 20 mm Hg in SBP or at least 10 mm Hg in DBP when a patient moves from a sitting to a standing position) were observed in 21 patients (4.7%) in the 5/160 mg treatment regimen and 30 patients (6.7%) in the 10/160 mg treatment group. Orthostatic hypotension was reported as an adverse event in 3 patients (0.7%) receiving amlodipine/valsartan 5/160 mg and in 1 patient (0.2%) treated with amlodipine/valsartan 10/160 mg. There were no cases of serious orthostatic hypotension: no patients discontinued due to orthostatic hypotension.

DISCUSSION

In patients with hypertension uncontrolled with previous antihypertensive monotherapy, switching to a dual-mechanism treatment strategy with a CCB (amlodipine) and an ARB (valsartan) resulted in BP control rates >70% at study end (week 16); BP control was somewhat greater with amlodipine/valsartan 10/160 mg (74.8%) than with amlodipine/valsartan 5/160 mg (72.7%). Control rates in both treatment groups were better than those reported in another study involving low-dose CCB/ARB combination therapies in patients whose hypertension was uncontrolled with high-dose monotherapy,[14] perhaps due in part to a carry-over effect from monotherapy or a lack of a prespecified run-in period.

Incremental BP-lowering effects were achieved with both amlodipine/valsartan regimens; however, reductions from baseline in mean sitting BP levels were significantly greater with the higher dose compared with the lower dose (20.0 vs 17.5 mm Hg; *P*=.0003 for MSSBP [difference of 2.5 mm Hg] and 11.6 vs 10.4 mm Hg; *P*=.0046 for MSDBP [difference of 1.2 mm Hg], respectively). Similar reductions in BP values have been reported recently in patients with hypertension treated with amlodipine plus valsartan.[16] These responses are expected when one effective agent is added to another. After 4 weeks of treatment, the mean BP values reached in both groups were <140/90 mm Hg (Figures 2 and 4). This may be important because inappropriate delays in BP control or failure to maintain adequate BP control may increase cardiovascular event rates.[18,19]

Patients with uncontrolled BP at weeks 8 or 12 were obliged to have HCTZ added to their treatment regimen, but this add-on therapy was not necessary for the majority of patients (>70% in each treatment group at week 8). Those requiring HCTZ were mainly receiving amlodipine/valsartan 5/160 mg. Of note, the addition of HCTZ to amlodipine/valsartan after week 8 appeared to have little additional effect on BP in either treatment group; however, it must be remembered that only the patients with the most resistant hypertension received this add-on therapy.

Subgroup analysis demonstrated that the additional antihypertensive efficacy of the combination at either dose was well maintained regardless of

previous antihypertensive monotherapy, hypertension severity, diabetic status, BMI, or age. As expected, when analyzed by severity of hypertension, the magnitude of reduction in MSSBP was proportional to baseline BP. These findings are consistent with results reported in other studies evaluating the BP-lowering efficacy of antihypertensive agents.[17,20] BP control rates (<140/90 mmHg) in patients with diabetes were similar to those in nondiabetic patients.

A limitation of the present study is that results obtained after week 8 must be interpreted with caution because some patients were receiving HCTZ add-on therapy after this time point.

Adverse events occurred in 42.2% of patients in the amlodipine/valsartan 5/160 mg treatment group and in 56.2% of patients treated with the higher-dose combination. The proportions of patients who discontinued treatment were 8.1% and 17.1%, respectively, in the low- and high-dose groups, while the proportion of patients reporting headache, back pain, dizziness, and muscle spasms was comparable between the 2 regimens. The number of patients reporting peripheral edema in the amlodipine/valsartan 10/160 mg group was more than 3-fold greater than in the amlodipine/valsartan 5/160 mg group (25.1% vs 8.1%). The edema rates reported in this study are higher than those reported in other studies involving similar doses of these agents.[15,20] Edema remains the most frequent adverse event associated with amlodipine and other long-acting dihydropyridine CCBs.[21] Frequencies of peripheral edema as high as 70% have been reported in various studies with CCBs.[22] Other studies involving amlodipine 10 mg monotherapy[18,23,24] have reported higher frequencies of peripheral edema than were found with amlodipine/valsartan 10/160 mg in this study, suggesting that ARBs may attenuate, but not eliminate, amlodipine-induced peripheral vasodilatory edema.[16,17,21]

CONCLUSIONS

These results provide additional support for the rationale of combining antihypertensive drugs with complementary mechanisms of action for the treatment of patients with hypertension. These data add to the literature indicating that combination therapy lowers BP to a greater degree than monotherapy. Amlodipine/valsartan was found to be an effective and well-tolerated strategy for BP control in a wide range of patients with hypertension not previously controlled by use of a single antihypertensive agent.

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