Effects of the Angiotensin Receptor Blocker Azilsartan Medoxomil Versus Olmesartan and Valsartan on Ambulatory and Clinic Blood Pressure in Patients With Stages 1 and 2 Hypertension

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Abstract—Azilsartan medoxomil is an angiotensin receptor blocker (ARB) being developed for hypertension treatment. To compare this ARB with others in the class, we studied the effects of 2 doses of azilsartan medoxomil, with valsartan 320 mg and olmesartan medoxomil (olmesartan) 40 mg, in a randomized, double-blind, placebo-controlled trial using ambulatory blood pressure (BP) monitoring and clinic BP measurements. The primary efficacy end point was the change from baseline in 24-hour mean systolic BP. Hierarchical analysis testing for superiority over placebo was followed by noninferiority analysis and then superiority testing of azilsartan medoxomil (80 mg and then 40 mg) versus the comparator ARBs. For 1291 randomized patients, mean age was 56 years, 54% were men, and baseline 24-hour mean systolic BP was 145 mm Hg. Azilsartan medoxomil at 80 mg had superior efficacy to both valsartan at 320 mg and olmesartan at 40 mg: placebo-adjusted 24-hour systolic BP was lowered (−14.3 mm Hg) more than 320 mg of valsartan (−10.0 mm Hg; $P<0.001$) and 40 mg of olmesartan (−11.7 mm Hg; $P=0.009$). Azilsartan medoxomil at 40 mg was noninferior to 40 mg of olmesartan (difference: −1.4 mm Hg [95% CI: −3.3 to 0.5]). For clinic systolic BP, both doses of azilsartan medoxomil were superior to the comparator ARBs. Safety and tolerability were similar among the placebo and 4 active treatments. These data demonstrate that azilsartan medoxomil at its maximal dose has superior efficacy to both olmesartan and valsartan at their maximal, approved doses without increasing adverse events. Azilsartan medoxomil could provide higher rates of hypertension control within the ARB class. **(*Hypertension*. 2011;57:413-420.) ● Online Data Supplement**

Key Words: ambulatory blood pressure ■ angiotensin receptor blockers ■ azilsartan medoxomil ■ clinical trial ■ olmesartan ■ valsartan

Improved control of blood pressure (BP) in patients with hypertension is required to produce the maximum reduction in clinical cardiovascular events,[1,2] and expert consensus guidelines advocate BP levels <140/90 mm Hg in patients lacking target organ involvement and <130/80 mm Hg in patients with diabetes mellitus, heart disease, or kidney disease.[3,4] During the past decade, the use of angiotensin II receptor blockers (ARBs) has become a popular strategy in the management of hypertension, because they are effective in reducing BP and demonstrate tolerability profiles similar to placebo.[5,6] In addition, clinical outcome trials have shown that the ARBs reduce the proportion of hypertensive patients who develop type 2 diabetes mellitus and improve cardiovascular outcomes in such conditions as high-risk hypertension,[7,8] heart failure,[9] and diabetic kidney disease.[10,11]

Azilsartan medoxomil is a prodrug that is quickly hydrolyzed to the active moiety azilsartan, a potent and highly selective ARB with estimated bioavailability of 60% and elimination half-life of 12 hours.[12] The other major metabolite, M-II, is formed via CYP2C9 and has low affinity for the angiotensin II type 1 receptor. On the basis of dose-ranging studies and supporting pharmacokinetic data, the expected plateau of BP reduction for azilsartan medoxomil in the large majority of patients with hypertension is 40 or 80 mg once daily.[12] The present study was designed to evaluate both the efficacy and safety of this new ARB in comparison with placebo and the maximal, approved doses of olmesartan medoxomil (olmesartan; 40 mg once daily) and valsartan (320 mg once daily). A novel aspect of the study program was that the primary efficacy end point was the 24-hour mean systolic BP, whereas effects on BP in the clinic and the diastolic BPs were secondary measures.

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00696436).

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Methods

Study Design

The study was a randomized, double-blind, multicenter, placebo- and active-controlled trial, designed to evaluate the efficacy and safety of azilsartan medoxomil, 40 or 80 mg, compared with placebo, olmesartan, and valsartan in patients with hypertension after 6 weeks of treatment. After a 3- to 4-week washout of previous antihypertensive therapy and a coincident 2-week single-blind, placebo run-in period, eligible patients with hypertension were randomly assigned to placebo, 20 or 40 mg of azilsartan medoxomil, 160 mg of valsartan, or 20 mg of olmesartan once daily for 2 weeks. At the end of the 2 weeks, patients were force-titrated to 40 or 80 mg of azilsartan medoxomil, 320 mg of valsartan, 40 mg of olmesartan, or continuation of placebo once daily for an additional 4 weeks.

Clinical assessments, including seated BPs, were performed at baseline and at 2, 4, and 6 weeks postrandomization. Ambulatory BP recordings were performed at baseline and at the end of 6 weeks postrandomization.

Patients

Patients were recruited from 141 centers in Guatemala, Mexico, Peru, Puerto Rico, and the United States. Before initiation in the study, all of the patients were informed of the details of the study and signed consent forms approved by regional institutional review boards. The protocol conformed to the Declaration of Helsinki. Men and women ≥18 years of age with hypertension were included if their clinic systolic BP was ≥150 mm Hg and ≤180 mm Hg and if their 24-hour mean systolic BP was ≥130 mm Hg and ≤170 mm Hg.

Exclusion criteria included known or suspected secondary hypertension; severe diastolic hypertension (seated diastolic BP: >114 mm Hg); clinically significant renal (estimated glomerular filtration rate: <30 mL/min per 1.73 m^2) metabolic, hepatic, or psychiatric disorders; clinically relevant or unstable cardiovascular diseases; and type 1 or poorly controlled type 2 diabetes mellitus (hemoglobin A1c: ≥8%).

In addition, night-shift workers, pregnant or nursing women, and women of childbearing potential not using medically approved means of contraception were excluded from study participation. Any antihypertensive or concomitant medications known to affect BP were not permitted during the study.

BP Monitoring Assessments

Clinic BP measurements were made in triplicate in the nondominant arm after the patient was seated for 5 minutes using a semiautomated digital BP recorder (Omron HEM 705-CP). Every effort was made to ensure that the clinic BP readings were taken ≈24 hours after the previous dose of study medication and before any procedures, including venipuncture.

Ambulatory BP measurements were obtained with the SpaceLabs 90207 monitor (SpaceLabs, Inc). Quality criteria used for an acceptable ambulatory BP recording included the following: (1) monitoring period ≥24 hours in duration; (2) minimum of 80% of the BP readings expected during the 24-hour period; (3) no more than 2 nonconsecutive hours with <1 valid BP reading; and (4) no consecutive hours with <1 valid BP reading. If these criteria were not met, the patient was asked to repeat the procedure within 3 days. If the repeat study failed to meet the quality control criteria, the ambulatory BP data were considered nonevaluable.

During the 24-hour ambulatory monitoring study, BP was measured every 15 minutes between 6:00 AM and 10:00 PM and every 20 minutes between 12:00 AM and 6:00 AM. Monitoring hookup was initiated at 8:00 AM ±2 hours.

Medication Dosing

All of the subjects received 3 tablets of different sizes (20, 40, or 80 mg of active azilsartan medoxomil or respective placebos) and 1 capsule (for active olmesartan, active valsartan, or placebo). All of the medications were administered once daily in the morning.

Safety Assessments

Safety variables included all adverse events, clinical laboratory data, physical examination findings, electrocardiographic data, and pregnancy evaluation. With regard to adverse events, all of the patients were queried at every visit with nonleading questions. Adverse events were characterized as nonserious or serious and those leading to discontinuation from the study. With regard to laboratory data, changes in renal function, liver enzymes, and serum potassium values were parameters of interest and measured at all of the study time points.

Statistical Analyses

The primary end point for assessing efficacy was the change from baseline in the 24-hour mean systolic BP after 6 weeks of treatment. The key secondary end point was the change from baseline in trough, seated, clinic systolic BP; additional secondary end points included changes from baseline in the 24-hour mean and clinic diastolic BPs.

The primary analysis compared treatment effects on the primary efficacy end point and was based on an ANCOVA model that included treatment as a fixed effect and baseline 24-hour mean systolic BP as a covariate. The primary comparisons were performed among azilsartan medoxomil, valsartan, olmesartan, and placebo and used the mean squared error for all of the treatment comparisons and the 95% CIs of treatment difference in change from baseline between treatment groups. In addition, noninferiority analyses were performed for the comparison between azilsartan medoxomil and each of the active control arms.

The margin of noninferiority (1.5 mm Hg) was set to be less than one-third of the observed placebo adjusted treatment effect of the comparators.[13,14] Type 1 error for the primary end point was controlled by using a stepwise, hierarchal testing procedure as shown in Figure 1. A similar testing procedure for the key secondary end point was performed by assessing noninferiority to valsartan before the superiority to olmesartan for a given dose of azilsartan medoxomil. Analyses of subgroups by age, sex, race, and body mass index were performed for the primary and secondary end points.

The sample size for the trial was determined on the basis of ambulatory BP considerations. Assuming an SD of 13 mm Hg for the mean change from baseline on 24-hour mean systolic BP and a 15% dropout rate, 290 patients per active treatment group and 145 patients for the placebo group were sufficient to achieve ≥90% power to detect a difference of 5.5 mm Hg between azilsartan medoxomil and placebo and to detect a difference of 4 mm Hg between azilsartan medoxomil and the other active treatment groups. The sample size was also adequate to provide ≥90% power for demonstrating noninferiority with a margin of 1.5 mm Hg between azilsartan medoxomil and the active-controlled groups on both the primary (24-hour mean systolic BP) and key secondary (clinic systolic BP) efficacy end points.

Results

Patient Enrollment and Disposition

We screened 3560 patients for the study, and 2661 patients were enrolled in the single-blind, placebo run-in period. Of the 1291 patients who met the entry criteria and were randomized, 1285 received the following treatments: (1) 280 patients to 40 mg of azilsartan medoxomil; (2) 285 patients to 80 mg of azilsartan medoxomil; (3) 282 patients to 320 mg of valsartan; (4) 290 patients to 40 mg of olmesartan; and (5) 154 patients to placebo (Figure 2). As shown in Figure 2, 1175 of the 1291 randomized patients completed the study as planned. The most common reasons for discontinuing the study early were adverse events, voluntary withdrawal, and lack of efficacy.

Baseline Characteristics of the Study Population

The baseline characteristics of all of the randomized patients in the 5 treatment arms are shown in Table 1. For the entire patient population, the mean age was 56 years, with a greater percentage of men (54%), and patients were predominantly white (62% to 67%) and with mean baseline clinic BP of 156 to 158/92 to 93 mm Hg and 24-hour mean BP of 144 to 146/88 to 90 mm Hg. There were statistically significant but clinically unimportant imbalances in the

Step 1. Compare AZL-M 80 mg *vs* placebo at significance level of 5%. If a 2-sided P-value was not > 5%, proceed to Step 2.
Step 2. Compare AZL-M 40 mg *vs* placebo at significance level of 5%. If a 2-sided P-value was not > 5%, proceed to Step 3.
Step 3. Compare AZL-M 80 mg *vs* olmesartan 40 mg with non-inferiority margin of 1.5 mmHg. If the upper limit of the 2-sided 95% CI on the treatment difference (AZL-M minus olmesartan) was not > 1.5 mmHg, proceed to Step 4.
Step 4. Compare AZL-M 80 mg *vs* olmesartan 40 mg at significance level of 5%. If a 2-sided P-value was not > 5%, then proceed to Step 5.
Step 5. Compare AZL-M 80 mg *vs* valsartan 320 mg with non-inferiority margin of 1.5 mmHg. If the upper limit of the 2-sided 95% CI on the treatment difference (AZL-M minus valsartan) was not > 1.5 mmHg, proceed to Step 6.
Step 6. Compare AZL-M 80 mg *vs* valsartan 320 mg at significance level of 5%. If a 2-sided P-value was not > 5%, then proceed to Step 7.
Step 7. Compare AZL-M 40 mg *vs* olmesartan 40 mg with non-inferiority margin of 1.5 mmHg. If the upper limit of the 2-sided 95% CI on the treatment difference (AZL-M minus olmesartan) was not > 1.5 mmHg, proceed to Step 8.
Step 8. Compare AZL-M 40 mg *vs* olmesartan 40 mg at significance level of 5%. If a 2-sided P-value was not > 5%, then proceed to Step 9.
Step 9. Compare AZL-M 40 mg *vs* valsartan 320 mg with non-inferiority margin of 1.5 mmHg. If the upper limit of the 2-sided 95% CI on the treatment difference (AZL-M minus valsartan) was not > 1.5 mmHg, proceed to Step 10.
Step 10. Compare AZL-M 40 mg *vs* valsartan 320 mg at significance level of 5%

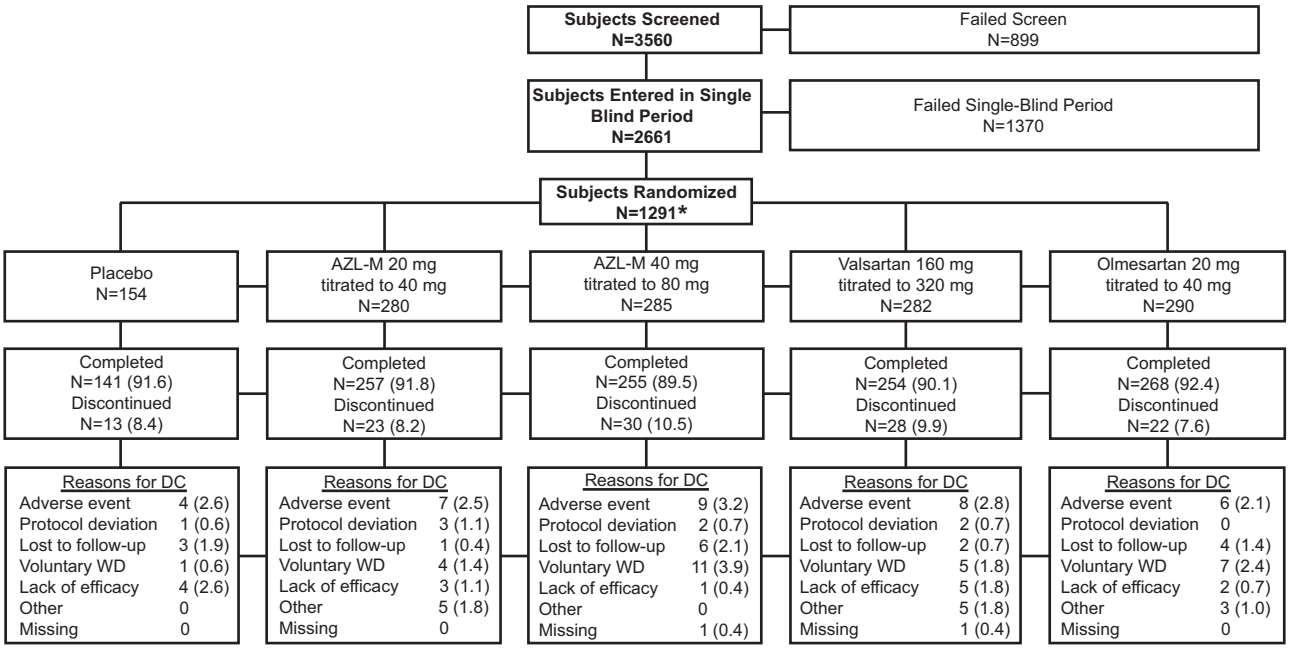
*Change from baseline 24-hour mean systolic blood pressure. AZL-M=azilsartan medoxomil.

Figure 1. Step-wise statistical testing procedure to control for type 1 error for the primary end point.*

baseline 24-hour mean and daytime diastolic BPs among the 5 treatment arms ($P=0.029$ and $P=0.027$, respectively) observed.

Changes in the 24-Hour Systolic BP

The effects of the 5 treatment groups on 24-hour mean systolic BPs are shown in Table 2 and Figure 3. All of the active therapies lowered 24-hour mean systolic BP significantly with mean differences from placebo ranging from −10.0 mm Hg for 320 mg of valsartan to −14.3 mm Hg for 80 mg of azilsartan medoxomil. Changes from baseline in 24-hour mean systolic BP were significantly greater with 80 mg of azilsartan medoxomil versus both 40 mg of olmesartan and 320 mg of valsartan, whereas 40 mg of azilsartan medoxomil was noninferior to 40 mg of olmesartan (Table 2). The pharmacodynamic effects of the various angiotensin receptor blockers and placebo after 6 weeks of therapy are shown in Figure 3. Hourly reductions in ambulatory systolic BP were lower than those of placebo at all of the time points in all 4 of the active therapy groups (Figure 3A). Azilsartan



Note: Data are no. (%). DC = discontinuation; WD = withdrawal
*Six subjects were randomized but not treated, and one subject was treated but not randomized.

Figure 2. Disposition of patients during the trial.

Table 1. Characteristics of the Randomized Patients at Baseline

Characteristic	Placebo (N=154)	AZL-M 40 mg (N=280)	AZL-M 80 mg (N=285)	Valsartan 320 mg (N=282)	Olmesartan 40 mg (N=290)
Age, y	56±11	57±12	56±11	55±11	56±11
Male/female, %	58/42	53/48	53/47	54/46	55/45
Race, n (%)*					
Native American	32 (21)	49 (18)	46 (16)	41 (15)	44 (15)
Black	27 (18)	51 (18)	49 (17)	51 (18)	54 (19)
White	96 (62)	177 (63)	190 (67)	189 (67)	191 (66)
Region, n (%)					
United States	122 (79)	226 (81)	234 (82)	238 (84)	234 (81)
Latin America	32 (21)	54 (19)	51 (18)	44 (16)	56 (19)
Body mass index, kg/m^2	30.5±5.4	31.7±6.0	30.7±5.9	31.1±5.5	31.1±5.5
Clinic BP, mm Hg	156/93±13/11	157/93±13/11	158/92±12/11	157/93±13/10	158/92±13/9
24-Hour mean BP, mm Hg	144/89±11/9	144/88±10/10	145/89±10/10	146/90±10/9	145/88±10/9
Daytime BP, mm Hg†	148/92±11/10	148/91±10/10	149/92±10/10	150/94±11/9	148/91±10/10
Nighttime BP, mm Hg‡	134/80±13/10	134/79±13/11	134/80±13/10	136/81±13/10	134/79±13/11

*Race categories were not mutually exclusive.
†Data were from 6:00 AM to 10:00 PM.
‡Data were from 12:00 AM to 6:00 AM.
AZL-M indicates azilsartan medoxomil.

medoxomil at 80 mg lowered ambulatory systolic BP to a larger extent than 320 mg of valsartan and 40 mg of olmesartan for most of the 24 hours (Figure 3B).

Changes in Clinic Systolic BP and Ambulatory and Clinic Diastolic BPs

The effects of the active treatments and placebo on clinic systolic BP at 2, 4, and 6 weeks postrandomization are shown in Table 3. Changes from baseline in the clinic systolic BP were small on placebo (−0.7 to −1.8 mm Hg) using the semiautomated in-clinic digital BP device. Changes from baseline in the clinic systolic BP were statistically significantly larger on both doses of azilsartan medoxomil compared with valsartan and olmesartan at 6 weeks (Table 3).

Changes in the ambulatory (Table S1, available in the online Data Supplement at http://hyper.ahajournals.org) and clinic (Table S2) diastolic BPs were similar to findings for the changes in the systolic BP. Changes in both 24-hour and clinic diastolic BPs were significantly greater on 80 mg of azilsartan medoxomil than both 320 mg of valsartan and 40 mg of olmesartan at the nominal significance level of 0.05, whereas 40 mg of azilsartan also lowered 24-hour and clinic diastolic BPs to a greater extent than 320 mg of valsartan (Tables S1 and S2).

Response Rates

The proportion of patients who achieved a reduction of clinic systolic BP to <140 mm Hg and/or a reduction of ≥20 mm Hg was significantly larger on 80 mg of azilsartan medoxomil (58%) compared with placebo (22%), 320 mg of valsartan

Table 2. Changes From Baseline in 24-Hour Mean Ambulatory Systolic BP

Parameter	Placebo (N=134)	AZL-M 40 mg (N=237)	AZL-M 80 mg (N=229)	Valsartan 320 mg (N=234)	Olmesartan 40 mg (N=254)
Baseline SBP, mm Hg	144.3 (0.9)	144.4 (0.6)	144.6 (0.7)	146.3 (0.6)	144.4 (0.6)
Change from baseline, mm Hg	−0.3 (0.9)	−13.4 (0.7)	−14.5 (0.7)	−10.2 (0.7)	−12.0 (0.7)
Mean difference vs placebo		−13.2	−14.3	−10.0	−11.7
95% CI		−15.4 to −10.9	−16.5 to −12.0	−12.2 to −7.7	−14.0 to −9.5
P value vs placebo		<0.001*	<0.001*	<0.001*	<0.001*
Mean difference vs olmesartan		−1.4	−2.5		
95% CI		−3.3 to 0.5	−4.4 to −0.6		
P value vs olmesartan		0.136	0.009*		
Mean difference vs valsartan		−3.2	−4.3		
95% CI		−5.1 to −1.3	−6.3 to −2.4		
P value vs valsartan		0.001	<0.001*		

Values are expressed as least significant mean from baseline and SE of the mean. AZL-M indicates azilsartan medoxomil; SBP, systolic BP.
*Data indicate significant difference at the 0.05 level and significant within the framework of the stepwise analysis for azilsartan medoxomil comparisons (see Figure 1); superiority of 40 mg of azilsartan vs 320 mg of valsartan was not examined, because the stepwise testing sequence was halted at a previous step.

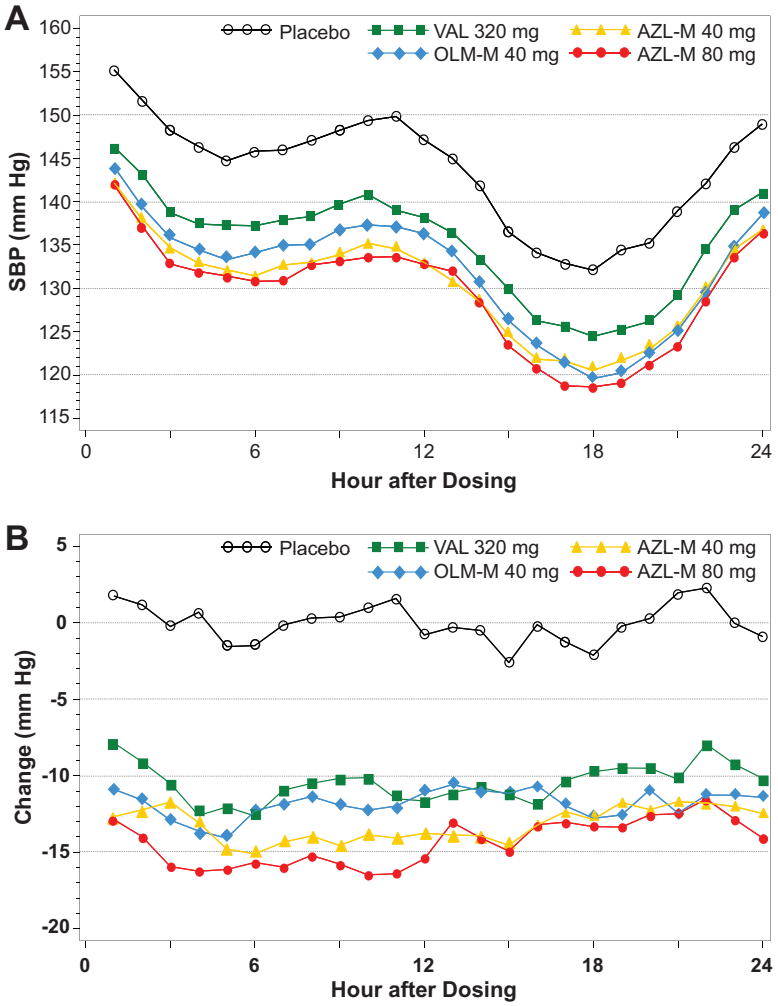


Figure 3. A, Hourly systolic BP after 6 weeks of treatment with placebo, 40 or 80 mg of azilsartan medoxomil (AZL-M), 320 mg of valsartan (VAL), and 40 mg of olmesartan (OLM-M). B, Changes from baseline in hourly systolic BP after 6 weeks of treatment with placebo, 40 or 80 mg of AZL-M, 320 mg of VAL, and 40 mg of OLM-M.

(49%), and 40 mg of olmesartan (49%) at the nominal significance level of 0.05.

Findings According to Age and Race

Reductions from baseline in ambulatory systolic BP were similar in men and women and in obese versus normal weight patients (data not shown). Changes from baseline in 24-hour mean systolic BP according to age and race are shown in Table 4. Reductions in 24-hour systolic BP between the 2 age groups were not statistically significant (*P* value of age-by-treatment interaction=0.74). There was a marginally statistically significant treatment difference between black and white patients (*P* value race-by-treatment interaction=0.06).

Safety and Tolerability

Of the 1286 patients who received ≥1 dose of study drug, a total of 635 (49.4%) had ≥1 adverse event with treatment during the 6-week double-blind period; these were distributed nearly equally among the 4 active treatment groups and placebo (Table 5). The most common adverse events during the trial were headache, dizziness, and urinary tract infection.

No deaths occurred during the study. Fourteen patients had a serious adverse event, and these were distributed nearly equally among the 5 treatment groups. Laboratory parameters of interest included changes in serum creatinine, potassium, and liver enzymes and had similar findings in the various treatment groups (Table 5). In a small proportion of patients (≤1.1%), serum creatinine increased by ≥50% above baseline in the 4 active treatment groups at any visit; no differences were observed between active groups. There were no instances of severe hyperkalemia (serum potassium: >6 mmol/L).

Discussion

Principal Findings

This is both the first phase 3, double-blind active comparator trial of the new ARB azilsartan medoxomil in patients with hypertension and the first phase 3 antihypertensive drug development program that used 24-hour ambulatory systolic BP monitoring for its primary efficacy end point. Azilsartan medoxomil at a dose of 80 mg once daily showed superior efficacy to both 320 mg of valsartan and 40 mg of olmesartan (their top approved doses for hypertension, respectively) using ambulatory and semiautomated in-clinic BP monitoring. The lower dose of azilsartan medoxomil (40 mg) was noninferior to 40 mg of olmesartan daily by 24-hour mean systolic BP. Both doses

Table 3. Changes From Baseline in Clinic Systolic BP

Parameter	Placebo (N=148)	AZL-M 40 mg (N=269)	AZL-M 80 mg (N=270)	Valsartan 320 mg (N=271)	Olmesartan 40 mg (N=283)
Baseline SBP, mm Hg	156.3 (1.0)	157.1 (0.8)	158.0 (0.8)	157.3 (0.8)	157.9 (0.7)
Change from baseline at week 2, mm Hg	−1.0 (1.2)	−12.7 (0.9)	−14.0 (0.9)	−8.8 (0.9)	−9.7 (0.9)
Change from baseline at week 4, mm Hg	−0.7 (1.2)	−16.4 (0.9)	−16.7 (0.9)	−10.8 (0.9)	−12.7 (0.9)
Change from baseline at week 6, mm Hg	−1.8 (1.3)	−16.4 (1.0)	−16.7 (1.0)	−11.3 (1.0)	−13.2 (0.9)
Difference vs placebo at week 6		−14.6	−14.9	−9.5	−11.4
95% CI		−17.7 to −11.4	−18.1 to −11.8	−12.6 to −6.3	−14.5 to −8.2
P value vs placebo		<0.001*	<0.001*	<0.001	<0.001
Difference vs olmesartan at week 6		−3.2	−3.5		
95% CI		−5.8 to −0.6	−6.2 to −0.9		
P value vs olmesartan		0.018*	0.008*		
Mean difference vs valsartan at week 6		−5.1	−5.4		
95% CI		−7.7 to −2.4	−8.1 to −2.8		
P value vs valsartan		<0.001*	<0.001*		

Values are expressed as least significant means and SE of the mean. AZL-M indicates azilsartan medoxomil.
*Data indicate significant difference at 0.001 level and significant within the framework of the stepwise analysis (see Figure 1).

of azilsartan medoxomil lowered clinic systolic BP to a greater extent than the comparator ARBs. Of note, these significant comparative reductions in BP on azilsartan were not associated with an increase in adverse events in comparison with the other active agents or with placebo. Hence, azilsartan medoxomil should be useful for the treatment of stages 1 and 2 hypertension and may be associated with superior rates of hypertension control.

Table 4. Impact of Age and Race on Changes From Baseline in Ambulatory Systolic BP

Group and Parameter	Placebo	AZL-M 40 mg	AZL-M 80 mg	Valsartan 320 mg	Olmesartan 40 mg
<65 y	N=102	N=176	N=180	N=193	N=193
Baseline mean	143.6 (1.0)	144.3 (0.7)	144.5 (0.7)	146.1 (0.7)	144.1 (0.7)
Change from baseline (SE), mm Hg	−0.65 (1.0)	−13.4 (0.8)	−14.6 (0.8)	−9.8 (0.8)	−12.1 (0.8)
Mean difference vs placebo		−12.7	−13.9	−9.2	−11.4
95% CI		−15.3 to −10.1*	−16.5 to −11.4*	−11.7 to −6.6*	−13.9 to −8.9
≥65 y	N=32	N=61	N=49	N=41	N=61
Baseline mean	146.5 (1.8)	144.9 (1.3)	145.0 (1.4)	147.6 (1.6)	145.3 (1.3)
Change from baseline (SE), mm Hg	0.9 (1.9)	−13.6 (1.4)	−14.2 (1.5)	−12.1 (1.7)	−11.8 (1.4)
Mean difference vs placebo		−14.5	−15.1	−13.0	−12.7
95% CI		−19.1 to −9.8*	−20.0 to −10.3*	−18.0 to −8.0*	−17.3 to −8.0*
White race	N=83	N=153	N=152	N=158	N=173
Baseline mean	143.8 (1.1)	144.3 (0.8)	144.6 (0.8)	146.2 (0.8)	144.8 (0.7)
Change from baseline (SE), mm Hg	0.6 (1.1)	−14.8 (0.8)	−16.2 (0.8)	−11.1 (0.8)	−12.7 (0.8)
Mean difference vs placebo		−15.4	−16.8	−11.7	−13.3
95% CI		−18.2 to −12.7*	−19.6 to −14.0*	−14.5 to −9.0*	−16.0 to −10.6*
Black race	N=24	N=40	N=37	N=38	N=42
Baseline mean	145.5 (2.0)	146.9 (1.5)	146.1 (1.6)	146.3 (1.6)	143.4 (1.5)
Change from baseline (SE), mm Hg	0.2 (2.0)	−7.4 (1.6)	−8.7 (1.6)	−4.3 (1.6)	−5.8 (1.5)
Mean difference vs placebo		−7.6	−8.9	−4.5	−6.0
95% CI		−12.7 to −2.5*	−14.0 to −3.8*	−9.6 to 0.6	−11.0 to −0.9*

*$P<0.05$. Values are expressed as least significant means and SE of the mean.
AZL-M indicates azilsartan medoxomil.

Table 5. Safety Findings According to Treatment Group

Parameter	Placebo (N=155)	AZL-M 40 mg (N=280)	AZL-M 80 mg (N=284)	Valsartan 320 mg (N=277)	Olmesartan 40 mg (N=290)
Total adverse events, N (%)	74 (47.7)	134 (47.9)	145 (51.1)	131 (47.3)	151 (52.1)
Adverse events leading to discontinuation, N (%)	3 (1.9)	7 (2.5)	8 (2.8)	7 (2.5)	6 (2.1)
Serious adverse events, N (%)	2 (1.3)	2 (0.7)	3 (1.1)	3 (1.1)	4 (1.4)
Treatment emergent events in >3% of any treatment group, N (%)					
Headache	14 (9.0)	18 (6.4)	12 (4.2)	21 (7.6)	23 (7.9)
Dizziness	4 (2.6)	10 (3.6)	10 (3.5)	5 (1.8)	9 (3.1)
Urinary tract infection	5 (3.2)	9 (3.2)	6 (2.1)	3 (1.1)	6 (2.1)
Fatigue	1 (0.6)	3 (1.1)	7 (2.5)	4 (1.4)	13 (4.5)
Edema, peripheral	1 (0.6)	5 (1.8)	4 (1.4)	9 (3.2)	8 (2.8)
Diarrhea	2 (1.3)	3 (1.1)	12 (4.2)	4 (1.4)	5 (1.7)
Laboratory abnormalities of interest					
Creatinine >1.5 baseline	0 (0)	2 (0.7)	3 (1.1)	1 (0.4)	2 (0.7)
Increased liver enzymes*	5 (3.3)	8 (2.9)	15 (5.5)	17 (6.1)	14 (4.9)
Potassium >6.0 mmol/L	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*Data show aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transpeptidase >3 times upper limit of normal. There were no deaths in the trial. AZL-M indicates azilsartan medoxomil.

Use of Ambulatory BP as a Primary Efficacy End Point

A unique aspect of this trial was the use of the 24-hour mean systolic BP as the primary efficacy end point rather than the mean clinic systolic or diastolic BP. To be included in the trial, patients were required to have a 24-hour systolic BP of ≥130 mm Hg, a value above which has been considered elevated and clinically important.[15,16] The avoidance of the inclusion of individuals with marked "white-coat" hypertension into the trial reduces the likelihood that antihypertensive drug effects over 24 hours will be "diluted."[17] Although the 24-hour systolic BP has been shown to be an important correlate of cardiovascular morbidity in patients with hypertension, it has not been used as the primary efficacy end point in the development of an antihypertensive agent. It is more challenging to demonstrate statistically significant benefits for antihypertensive agents when the systolic BP is used compared with the diastolic BP, particularly when comparative efficacy is involved. The larger variability of systolic BP both in the clinic and even with out-of-office measurements relative to the diastolic BP requires an increase in the sample size in a hypertension clinical trial.[18] Use of 24-hour ambulatory BP monitoring reduces this sample size requirement to a certain extent and is useful in comparing antihypertensive drugs, especially when assessing the time course of changes in BP. There are numerous examples in the literature that now illustrate this benefit, including the superiority of ambulatory over clinic BP in assessing the trough-to-peak ratio of various agents.[17,19] In the present trial, hourly reductions in systolic BP were greater on azilsartan medoxomil compared with the other active agents, in addition to the larger reductions in mean 24-hour ambulatory systolic BP.

Comparisons of BP-Lowering Trials Within the Same Antihypertensive Class

In nearly all of the cases in which antihypertensive drugs have been evaluated in the same class using the highest approved doses, ambulatory and clinic BP findings have been similar among the agents. Some exceptions to this observation are those agents that vary markedly in half-life, such as bisoprolol versus atenolol[20] or telmisartan versus losartan.[21] In fact, ambulatory BP monitoring was able to discern differences between telmisartan and losartan when the clinic BP was not able to consistently show these changes.[22]

The ability of ambulatory BP monitoring to detect these smaller changes between treatment groups compared with clinic BP is related to the lower variance that occurs with repeated ambulatory BP studies compared with repeated clinic BP measurements.[18,22] Because the reproducibility of ambulatory BP values is better than standard clinic BP values in middle-aged and older people, sample sizes typically can be reduced by 30% to 50% to demonstrate similar effect sizes.[18,22] The finding that azilsartan medoxomil lowered 24-hour systolic BP to a greater extent than 2 other agents in the same class is novel and suggests that the agent has greater potency, although a mechanism for this finding is unknown.

Another unique finding in this trial was that the changes from baseline in the various treatment groups for clinic and ambulatory BP measurements were similar. Indeed, changes in clinic BP were <1 to 2 mm Hg in the placebo group, a finding that is atypical of clinical trials in hypertension.[23,24] This result may be attributable in part to the use of semiautomated BP monitors in the study sites that required printing and recording the results from the device and entering them into the case report form. Simply using a semiautomatic device without requiring enduring documentation of the results may not always lead to parity between the clinic and ambulatory BP readings.[24]

Safety Findings

The potent antihypertensive effects of azilsartan medoxomil were not accompanied by increases in adverse events during this short-term trial. In addition, the number of serious adverse

events was low during the study and balanced among the 5 treatment groups. Laboratory findings did not suggest any clinically relevant changes in renal function or potassium homeostasis on azilsartan medoxomil relative to valsartan, olmesartan, or placebo in a hypertensive population without severe renal impairment.

Perspectives

Azilsartan medoxomil, a new angiotensin receptor blocker, has superior ambulatory and clinical BP-lowering effects compared with olmesartan and valsartan at their highest clinically used doses and is well tolerated in patients with hypertension. BP control and response rates by this drug at its highest dose are greater than other drugs in the same class by absolute rates of 8% to 10%. On the basis of these data, we would expect that azilsartan medoxomil could lead to enhanced BP control in patients with stages 1 to 2 hypertension. The latest evaluation of the National Health and Nutrition Examination Survey in the United States[25] estimates that 50.1% of patients with hypertension, with some variance according to age and ethnicity, are controlled. This finding represents a substantial improvement over the past 2 decades but still leaves half of the hypertensive population at risk for cardiovascular events. Although the efficacy and tolerability of antihypertensive drug therapy are not the only factors that play a role in hypertension control rates, they are likely among the most important. Hence, new drugs that are more efficacious and well tolerated could be effective in improving BP control in the hypertensive population.

The study results also demonstrate that the use of ambulatory BP as a primary efficacy end point is both feasible and increases the understanding of the pharmacodynamic behavior of not only the investigational drug under evaluation but known comparator agents as well. Using a standardized semiautomated device in the clinic in which a permanent record of the BP values was a requirement seems to improve the reliability of those values, as well as the agreement between the clinic-derived and ambulatory BP recording–derived BPs.

Disclosures

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EFFECTS OF THE ANGIOTENSIN RECEPTOR BLOCKER AZILSARTAN MEDOXOMIL VERSUS OLMESARTAN AND VALSARTAN ON AMBULATORY AND CLINIC BLOOD PRESSURE IN PATIENTS WITH STAGES 1-2 HYPERTENSION

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Table S1. Changes from Baseline in Ambulatory Diastolic Blood Pressure

Parameter	Placebo N = 134	Azilsartan 40 mg N = 237	Azilsartan 80 mg N = 229	Valsartan 320 mg N = 234	Olmesartan 40 mg N = 254
Baseline Diastolic BP (mmHg)	88.9 (0.8)	87.7 (0.6)	88.5 (0.6)	90.1 (0.6)	87.6 (0.6)
Change from baseline (mmHg)	- 0.1 (0.6)	-8.7 (0.5)	-9.4 (0.5)	-7.1 (0.5)	-7.7 (0.5)
Mean difference vs placebo		-8.6	-9.4	-7.0	-7.7
(95% CI)		(-10.1, -7.0)	(-10.9, -7.8)	(-8.6, -5.5)	(-9.2, -6.2)
p –value vs placebo		< 0.001*	< 0.001*	< 0.001*	< 0.001*
Mean difference vs olmesartan		-0.9	-1.7		
(95% CI)		(-2.2, 0.4)	(-3.0, -0.4)		
p value vs olmesartan		0.17	0.011*		
Mean difference vs valsartan		-1.6	-2.4		
(95% CI)		(-2.9, -0.2)	(-3.7, -1.0)		
p-value vs valsartan		0.020*	< 0.001*		

*indicates significant difference at 0.05 level
Values are expressed as LS mean and standard error of the mean (SE)

Table S2. Changes from Baseline in Clinic Diastolic Blood Pressure

Parameter	Placebo N = 148	Azilsartan 40 mg N = 269	Azilsartan 80 mg N = 270	Valsartan 320 mg N = 271	Olmesartan 40mg N = 283
Baseline Diastolic BP (mmHg)	93.7 (0.8)	92.1 (0.6)	92.1 (0.6)	93.3 (0.6)	91.9 (0.6)
Change from baseline at Week 2 (mmHg)	0.6 (0.7)	-5.2 (0.5)	-6.2 (0.5)	-3.2 (0.5)	-4.3 (0.5)
Change from baseline at Week 4 (mmHg)	0.1 (0.7)	-7.3 (0.5)	-8.3 (0.5)	-5.6 (0.5)	-5.9 (0.5)
Change from baseline at Week 6 (mmHg)	-0.8 (0.7)	-7.0 (0.6)	-8.3 (0.6)	-5.1 (0.6)	-6.1 (0.5)
Difference vs placebo at Week 6		-6.2	-7.5	-4.4	-5.3
(95% CI)		(-8.0, -4.4)	(-9.3, -5.7)	(-6.2, -2.5)	(-7.1, -3.5)
p –value vs placebo		< 0.001*	< 0.001*	< 0.001*	< 0.001*
Difference vs olmesartan at Week 6		-0.9	-2.2		
(95% CI)		(-2.4, 0.6)	(-3.7, -0.7)		
p value vs olmesartan		0.257	0.005*		
Mean difference vs valsartan at Week 6		-1.9	-3.2		
(95% CI)		(-3.4, -0.3)	(-4.7, -1.6)		
p-value vs valsartan		0.017*	< 0.001*		

*indicates significant difference at 0.05 level
Values are expressed as LS means and standard error of the mean (SE)