Original Paper

The Comparative Effects of Azilsartan Medoxomil and Olmesartan on Ambulatory and Clinic Blood Pressure

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*The current study assesses the antihypertensive efficacy and safety of the investigational angiotensin receptor blocker (ARB), azilsartan medoxomil (AZL-M), compared with placebo and the ARB olmesartan medoxomil (OLM-M). This randomized, double-blind, placebo-controlled, multicenter study assessed change from baseline in mean 24-hour ambulatory systolic blood pressure (SBP) following 6 weeks of treatment. Patients with primary hypertension (*n=*1275) and baseline 24-hour mean ambulatory systolic pressure ≥130 mm Hg and ≤170 mm Hg were studied; 142 received placebo and the remainder received 20 mg, 40 mg, or 80 mg AZL-M or 40 mg OLM-M. Mean age of participants was 58±11 years, baseline mean 24-hour SBP was 146 mm Hg. Dose-dependent reductions in 24-hour mean SBP at study end occurred in all AZL-M groups. Reduction in 24-hour mean SBP was greater with AZL-M 80 mg than OLM-M 40 mg by 2.1 mm Hg (95% confidence interval, −4.0 to −0.1;* P=.*038), while AZL-M 40 mg was noninferior to OLM-M 40 mg. The side effect profiles of both ARBs were similar to placebo. AZL-M is well tolerated and more efficacious at its maximal dose than the highest dose of OLM-M.* J Clin Hypertens (Greenwich). *2011;13:81–88.* ©*2011 Wiley Periodicals, Inc.*

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Hypertension affects an estimated 74.5 million individuals in the United States.[1] Despite the availability of antihypertensive treatments, hypertension remains inadequately controlled, with slightly less than half of patients who receive treatment successfully achieving blood pressure (BP) goals.[2] While there are many drug classes available to reduce BP, drugs that modulate the renin-angiotensin-aldosterone system (RAAS) are more commonly used because of their efficacy, coupled with one of the lowest side effect profiles.[3] Moreover, within the RAAS classes, those that inhibit the action of angiotensin II by binding directly to the angiotensin type 1 (AT_1) receptor (ie, angiotensin receptor blockers [ARBs]) are the best tolerated of all antihypertensive drug classes.[3] Some ARBs have shown efficacy in reducing mortality in patients with heart failure and post–myocardial infarction as well as slowing progression of diabetic nephropathy.[4–8]

Azilsartan medoxomil (AZL-M) is an investigational ARB in development for the treatment of hypertension. It is a prodrug that is rapidly hydrolyzed to its active moiety, azilsartan. This paper presents data on the efficacy and safety of different AZL-M doses compared with placebo and an established ARB.

METHODS

This study (trial registration: NCT00696241) used a randomized, multicenter, parallel group, double-blind, placebo-controlled design to evaluate the antihypertensive efficacy and safety of AZL-M in patients with primary hypertension. Efficacy was assessed with both ambulatory BP monitoring (ABPM) and BP measurements obtained in the clinic. The planned sample size was 1260 participants. Before randomization, patients received placebo for a 2-week run-in period. For patients who previously received antihypertensive treatment, the run-in period coincided with a 3- to 4-week washout of other antihypertensive medications to establish a treatment-free baseline BP. After the washout/run-in period, eligible patients were randomized to 6 weeks of double-blind treatment. Randomization was stratified by race (ie, black or non-black).

Patient Eligibility

Participants from 140 centers in the United States, Peru, Argentina, and Mexico were enrolled in the trial. Inclusion criteria included a diagnosis of primary hypertension (defined as sitting trough clinic systolic BP [SBP] $\geq$150 mm Hg and $\leq$180 mm Hg and 24-hour mean SBP $\geq$130 mm Hg and $\leq$170 mm Hg) prior to randomization. Men and women 18 years or older who were capable of complying with protocol requirements were enrolled. Each patient signed an institutional review board–approved informed consent form before initiation of any study procedures. Sexually active women of childbearing potential agreed to use adequate contraception throughout the study. Each eligible patient's screening clinical laboratory test results were within the reference range for the testing laboratory or, if out of range, were deemed not clinically significant by the investigator.

Patients were excluded for the following: sitting clinic diastolic BP (DBP) >114 mm Hg, history of major cardiovascular events, significant cardiac conduction defects, secondary hypertension, poor compliance during the placebo run-in period, severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), known or suspected renal artery stenosis, type 1 or poorly controlled type 2 diabetes, significant hepatic abnormalities, hyperkalemia, or a baseline ABPM reading of insufficient quality.

End Points

The primary end point was change in 24-hour mean systolic BP at week 6 as assessed by ABPM. The key secondary end point was change in trough sitting clinic systolic BP at week 6. Other secondary end points included change from baseline in the following parameters: 24-hour mean DBP by ABPM, trough sitting clinic DBP, and other ABPM parameters of SBP and DBP (daytime mean [6 AM–10 PM], nighttime mean [12 AM–6 AM], mean at 0 to 12 hours after dosing, and mean at trough [22–24 hours after dosing]). The proportion of responders was also evaluated, with "responder" defined as a patient whose clinic SBP reached a target of <140 mm Hg and/or was reduced by $\geq$20 mm Hg from baseline. Safety end points included adverse events, safety laboratory tests, electrocardiographic findings, and vital signs.

Procedures

ABPM was performed at baseline and the final visit using a portable, automated device (model 90207; Spacelabs, Inc, Issaquah, WA). The baseline ABPM was performed during the 24-hour period before randomization, and the final-visit ABPM was performed during the 24 hours after the final dose of double-blind treatment (6 weeks). In each instance, BP was measured every 15 minutes between 6 AM and 10 PM and every 20 minutes between 10 PM and 6 AM. Minimum quality-control criteria included monitoring period $\geq$24 hours, minimum of 80% of expected BP readings, no more than 2 nonconsecutive hours with <1 valid BP reading, and no consecutive hours with <1 valid BP reading. If either ABPM measurement was unsuccessful, it could have been repeated once within 5 or 4 days (for baseline or final ABPM, respectively) with extension of study medication for the purposes of capturing the ABPM data.

Office BP was measured at each study visit (baseline and at 2, 4, and 6 weeks post-randomization) with an automated sphygmomanometer (Omron HEM 705-CP, Vernon Hills, IL) approximately 24 hours after the previous dose of study medication. The average of 3 BP measurements was recorded at least 5 minutes after the patient had been seated.

At each visit, the investigator assessed whether the patient had experienced any adverse events, and

the patient could report events spontaneously throughout the study. Each event was categorized as nonserious or serious and whether it resulted in discontinuation of treatment. Safety laboratory tests were analyzed by a central laboratory (ICON Laboratories, Farmingdale, NY).

Statistics

Sample Size. Approximately 1260 randomized patients (280 to AZL-M and olmesartan medoxomil [OLM-M] treatment groups and 140 to the placebo treatment group) were determined as sufficient to achieve at least 90% power to detect a difference of 5.5 mm Hg between the AZL-M treatment groups and placebo for the primary end point, assuming a 2-sided significance level of 5%, a standard deviation of 13 mm Hg, and a 15% dropout rate. This sample size also provided approximately 90% power to detect a difference of 4 mm Hg between AZL-M and OLM-M by a 2-sample *t* test for the primary end point, with a 2-sided significance level of 5%. There was at least 90% power for demonstrating noninferiority with a margin of 1.5 mm Hg between AZL-M and OLM-M for the primary end point.

Analysis of End Points. The primary end point was evaluated using an analysis of covariance (ANCOVA) with treatment as fixed effect and its baseline value as covariate. Comparisons were made between AZL-M and placebo and between AZL-M and OLM-M according to a step-wise testing procedure to control for type 1 error, with both noninferiority and superiority tests for the latter comparison. All statistical tests were 2-sided and results were presented as 95% confidence intervals (CIs) and *P* values at a 5% significance level. The noninferiority margin was set at 1.5 mm Hg, which is less than one third of the placebo-adjusted treatment effects of OLM-M.[9] The comparisons between AZL-M and placebo and the noninferiority and superiority comparisons between AZL-M and OLM-M proceeded as follows: AZL-M 80 mg, 40 mg, and 20 mg vs placebo (proceed if *P* value $\leq$5% for all doses), AZL-M 80 mg and 40 mg vs OLM-M (proceed if AZL-M is noninferior to OLM-M for both doses), AZL-M 80 mg and 40 mg vs OLM-M (proceed if *P* value $\leq$5% for both doses), AZL-M 20 mg vs OLM-M (proceed if AZL-M is noninferior to OLM-M), and AZL-M 20 mg vs OLM-M at a significance level of 5%.

The same statistical model, testing procedure, and noninferiority margin was used for the analysis of the key secondary end point, trough clinic sitting SBP. Other secondary analyses of continuous variables used a similar ANCOVA model, but without the stepwise testing procedure. A logistic model with treatment as fixed effect and baseline value as a covariate was used in the analysis of responder rates. An odds ratio and its 95% CI were estimated. The analyses for clinic SBP, clinic DBP, and responder rate were based on the last-observation-carried-forward (LOCF) method.

Subgroup analyses were performed by age (younger than 65, 65 years or older), sex, race (self-identified as black, white, other), baseline 24-hour mean SBP (<median, $\geq$median), body mass index (BMI) (<30 kg/m^2, $\geq$30 kg/m^2), and kidney function (eGFR $\geq$90 mL/min/1.73 m^2, $\geq$60 mL/min/1.73m^2 to <90 mL/min/1.73 m^2, $\geq$30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2).[10]

RESULTS

Patient Disposition and Demographics

A summary of the patients recruited and the number who completed the trial is summarized in Figure 1. More than 90% of randomized patients completed the 6-week double-blind study while taking medication. The most common reasons for withdrawal were adverse events, voluntary withdrawal, and lack of efficacy.

Baseline characteristics of the cohort studied are summarized in Table I. There were no major differences between the groups. The percentage of patients 65 years or older was 29.5%, and the mean age was 58$\pm$11 years. The proportion of men and women was similar and 11% of patients were black. Approximately half of patients had mild or moderate renal impairment.

Changes in 24-Hour Mean Systolic and Clinic BP

The absolute changes from baseline for the primary and prespecified secondary end point are shown in Figure 2. Baseline values were similar across treatment groups, and there were dose-related decreases in both end points in the AZL-M treatment groups. Based on the step-wise statistical analysis plan, the change in 24-hour SBP was significantly greater when AZL-M 80 mg was compared with OLM-M 40 mg, while AZL-M 40 mg was noninferior to OLM-M 40 mg. The treatment difference between AZL-M 80 mg and OLM-M 40 mg was −2.1 mm Hg (95% CI, −4.0 to −0.1; *P*=.038), and the treatment difference between AZL-M 40 mg and OLM-M 40 mg was −0.92 mm Hg (95% CI, −2.87 to 1.02; *P*=.352). Moreover, while mean 24-hour baseline BPs were similar (149.5$\pm$1 mm Hg AZL-M vs 150.6$\pm$1 mm Hg OLM-M), the early

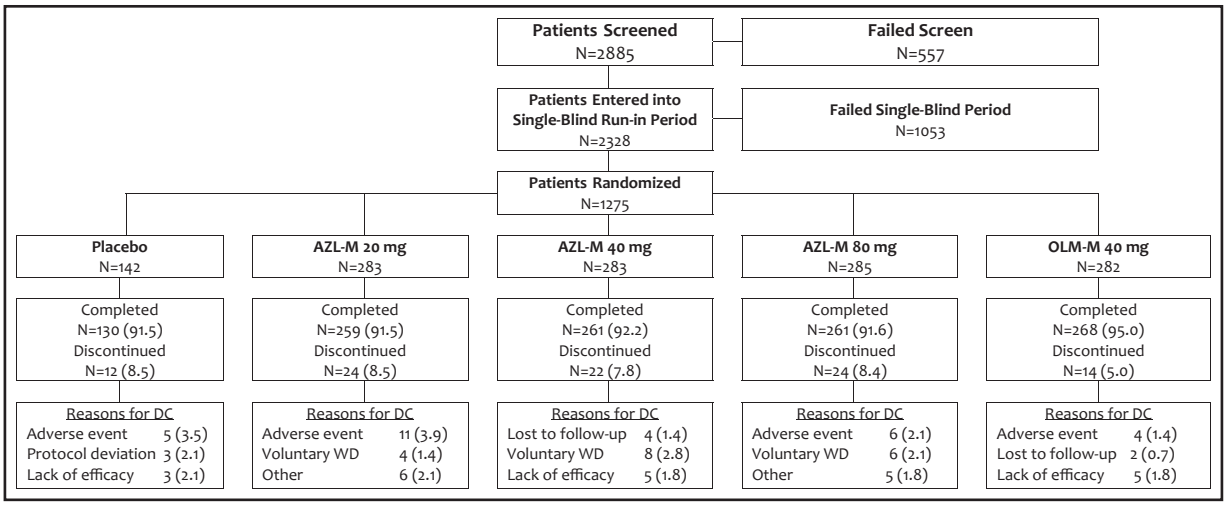

Figure 1. Patient disposition. Data are number (percentage). AZL-M indicates azilsartan medoxomil; OLM-M, olmesartan medoxomil; DC, discontinuation; WD, withdrawal. The 3 most common reasons for discontinuation are listed.

Table I. Demographics and Baseline Characteristics of Randomized Patients

	Treatment					
Characteristic	Placebo (N=142)	AZL-M 20 mg (N=283)	AZL-M 40 mg (N=283)	AZL-M 80 mg (N=285)	OLM-M 40 mg (N=282)	Total (N=1275)
Sex, No. (%)						
Male	76 (53.5)	133 (47.0)	142 (50.2)	149 (52.3)	140 (49.6)	640 (50.2)
Female	66 (46.5)	150 (53.0)	141 (49.8)	136 (47.7)	142 (50.4)	635 (49.8)
Age, mean (SD), y	59.4 (10.53)	57.1 (11.02)	57.4 (9.62)	58.1 (11.56)	58.9 (11.57)	58.0 (10.94)
Race, No. (%)[a]						
American Indian or Alaska Native	29 (20.4)	51 (18.0)	49 (17.3)	52 (18.2)	50 (17.7)	231 (18.1)
Asian	3 (2.1)	7 (2.5)	7 (2.5)	4 (1.4)	4 (1.4)	25 (2.0)
Black or African American	16 (11.3)	32 (11.3)	31 (11.0)	31 (10.9)	31 (11.0)	141 (11.1)
White	103 (72.5)	202 (71.4)	205 (72.4)	209 (73.3)	209 (74.1)	928 (72.8)
Multiracial	9 (6.3)	10 (3.5)	9 (3.2)	10 (3.5)	11 (3.9)	49 (3.8)
Weight, kg						
Mean (SD)	83.4 (18.95)	84.2 (21.53)	84.6 (20.37)	83.5 (19.61)	82.9 (19.63)	83.7 (20.13)
BMI, mean (SD), kg/m^2	30.0 (4.93)	30.4 (5.67)	30.6 (5.94)	30.0 (5.48)	29.8 (5.25)	30.2 (5.52)

Abbreviations: AZL-M, azilsartan medoxomil; BMI, body mass index; OLM-M, olmesartan medoxomil; SD, standard deviation.
[a]Patients may have chosen more than one category for race. These patients are included in each category indicated and in the multiracial category.

morning mean BP at week 6 demonstrated a trend for greater reduction by AZL-M 80 mg over OLM-M 40 mg (−12.2 mm Hg AZL-M vs −9.9 mm Hg OLM-M; *P*=.054). A similar trend was observed for other SBP parameters by ABPM, including mean daytime and nighttime BP. Reductions in ambulatory SBP were sustained throughout the 24-hour monitoring interval (Figure 3).

Results for change in clinic SBP at week 6 were consistent with the primary end point. Placebo-subtracted reductions in clinic SBP were −12.2 (95% CI, −15.5 to −9.0), −12.4 (95% CI, −15.6 to −9.2), and −15.5 mm Hg (95% CI, −18.7 to −12.3) with AZL-M 20 mg, 40 mg, and 80 mg and −12.8 mm Hg (95% CI, −16.0 to −9.6) with OLM-M 40 mg. As with 24-hour mean SBP, AZL-M 80 mg yielded a greater reduction in clinic SBP than OLM-M 40 mg, with a treatment difference of −2.7 mm Hg (95% CI, −5.3 to −0.1; *P*=.043). As shown in Figure 4, reductions in clinic

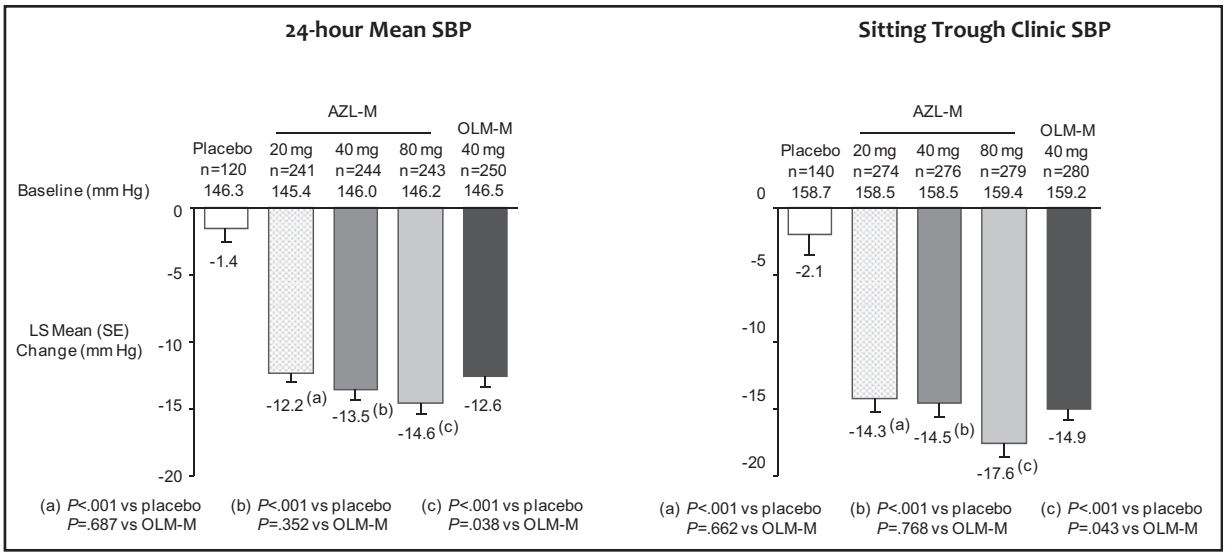

Figure 2. Change from baseline in 24-hour mean systolic blood pressure (SBP) and clinic SBP at study end. Superiority of azilsartan medoxomil (AZL-M) 80 mg vs olmesartan medoxomil (OLM-M) 40 mg was not examined for clinic SBP because the stepwise analysis was terminated at the comparison of AZL-M 40 mg vs OLM-M for noninferiority. LS indicates least-squares; SE, standard error of the mean.

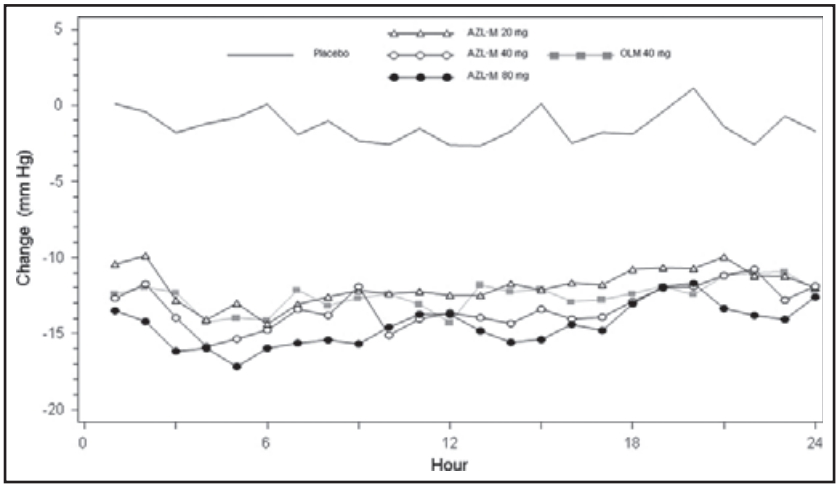

Figure 3. Change from baseline in ambulatory systolic blood pressure by hour at study end. AZL-M indicates azilsartan medoxomil; OLM-M, olmesartan medoxomil.

BP reached a plateau in the AZL-M and OLM-M treatment groups by week 4.

Changes in DBP

Changes in 24-hour mean DBP and clinic DBP were consistent with the results for SBP. Placebo-subtracted changes from baseline in 24-hour mean DBP were −6.8 mm Hg, −7.7 mm Hg, and −7.9 mm Hg with AZL-M 20 mg, 40 mg, and 80 mg, respectively, and −7.0 mm Hg with OLM-M 40 mg. Placebo-subtracted reductions in clinic DBP were −7.0 mm Hg, −7.1 mm Hg, −8.6 mm Hg, and −7.1 mm Hg, respectively. The reduction in clinic DBP was greater with the 80-mg dose of AZL-M compared with OLM-M 40 mg, with a treatment difference of −1.5 mm Hg (95% CI, −3.0 to −0.04; *P*=.044).

Responder Rates

The proportion of patients who had a reduction in clinic SBP to <140 mm Hg and/or a reduction of ≥20 mm Hg were 48%, 50%, and 57% with AZL-M 20 mg, 40 mg, and 80 mg, respectively, and 53% with OLM-M 40 mg. The comparative efficacy between AZL-M 80 mg and OLM-M

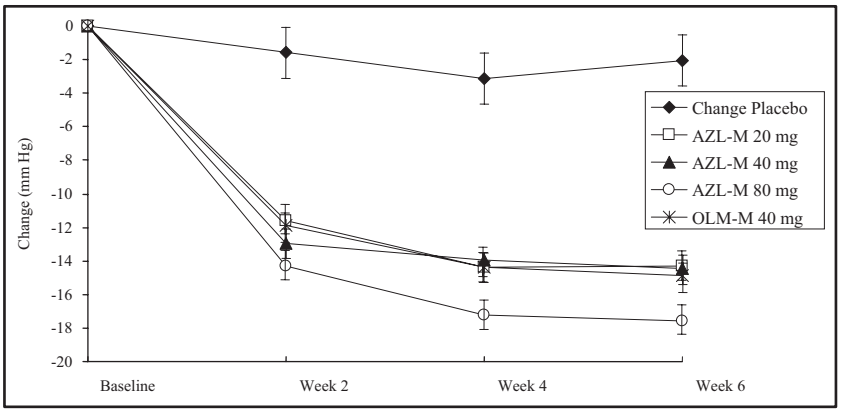

Figure 4. Change from baseline in clinic systolic blood pressure by study visit. Includes all patients with baseline and post-baseline values with the last observation carried forward. AZL-M indicates azilsartan medoxomil; OLM-M, olmesartan medoxomil.

40 mg yielded an odds ratio of 1.15 (95% CI, 0.83–1.62; *P*=.402).

Subgroup Analyses

Results of the subgroup analyses by age, sex, baseline median 24-hour mean SBP, and baseline eGFR did not reveal any interaction (data not shown). In the subgroup analysis by race, there was a moderately decreased effect among black patients compared with the non-black subgroups with all active treatments. Among black patients the placebo-subtracted change from baseline in 24-hour mean SBP was −4.0 mm Hg (95% CI, −10.8 to 2.8), −5.2 (95% CI, −12.3 to 1.8), and −5.1 mm Hg (95% CI, −11.9 to 1.7) with AZL-M 20 mg, 40 mg, and 80 mg, respectively and −3.0 mm Hg (95% CI, −9.8 to 3.7) with OLM-M 40 mg. The treatment difference between AZL-M 80 mg and OLM-M 40 mg was −2.1 mm Hg (95% CI, −7.7 to 3.5).

In the subgroup analysis by BMI, the placebo-subtracted change from baseline in 24-hour mean SBP for patients with BMI $\geq$30 kg/m^2 was −9.8 (95% CI, −13.6 to −6.0), −11.9 (95% CI, −15.6 to −8.2), and −13.6 mm Hg (95% CI, −17.5 to −9.8) with AZL-M 20 mg, 40 mg, and 80 mg and −10.9 mm Hg (95% CI, −14.7 to −7.1) with OLM-M 40 mg. The treatment difference between AZL-M 80 mg and OLM-M 40 mg was −2.7 mm Hg (95% CI, −5.8 to 0.32). Corresponding decreases among patients with BMI $<$30 kg/m^2 were −11.4 (95% CI, −14.6 to −8.3), −11.9 (95% CI, −15.1 to −8.8), −12.8 mm Hg (95% CI, −15.9 to −9.7) with AZL-M 20 mg, 40 mg, and 80 mg, and −11.1 mm Hg (95% CI, −14.2 to −8.0) with OLM-M 40 mg. The treatment difference between AZL-M 80 mg and OLM-M 40 mg was −1.7 mm Hg (95% CI, −4.2 to 0.9).

Adverse Effects

The most commonly reported adverse events in all groups were headache, dyslipidemia, and dizziness, and these were reported similarly in all treatment groups (Table II). Discontinuations due to adverse events and serious adverse events were reported more frequently in the placebo and AZL-M 20 mg groups. Serious events were reported in $<$1% of patients in the other groups. There were no major differences among groups with respect to clinical laboratory findings, including lipids and other metabolic variables (data not shown).

DISCUSSION

The results of this trial indicate that AZL-M is an efficacious and well-tolerated ARB that has BP-lowering effects greater than OLM-M when the highest doses of both were compared. Moreover, this greater efficacy is not associated with a worse adverse effect profile, as treatment at all doses yielded side effects no different from those observed in the placebo group.

Differences between groups in office SBP of 2 mm Hg to 3 mm Hg or more in both epidemiologic analyses and interventional trials is associated with greater cardiovascular risk reduction.[11] In this trial, we note a 2.1-mm Hg difference in SBP based on 24-hour ABPM, which may be clinically relevant based on previous meta-analyses demonstrating reduced cardiovascular risk with this magnitude of change.[12] Additionally, this incremental SBP-lowering effect was noted predominantly in obese people without diabetes, a growing portion of the population.[13] Given the neutral metabolic profile of ARBs and the efficacy of AZL-M over OLM-M for BP reduction, AZL-M affords the possibility of evaluating this agent as a way to help achieve BP goal and reduce

Table II. Summary of AEs

	Placebo (n=142)	AZL-M 20 mg (n=283)	AZL-M 40 mg (n=281)	AZL-M 80 mg (n=284)	OLM-M 40 mg (n=282)
Patients with any AE	51 (35.9)	109 (38.5)	101 (35.9)	117 (41.2)	107 (37.9)
Most common AEs					
Headache	10 (7.0)	13 (4.6)	9 (3.2)	16 (5.6)	9 (3.2)
Dyslipidemia	3 (2.1)	10 (3.5)	11 (3.9)	16 (5.6)	10 (3.5)
Dizziness	4 (2.8)	8 (2.8)	6 (2.1)	8 (2.8)	10 (3.5)
AE leading to discontinuation	6 (4.2)	11 (3.9)	3 (1.1)	6 (2.1)	4 (1.4)
Serious AE	3 (2.1)	8 (2.8)	0	1 (0.4)	2 (0.7)
Death[a]	0	1 (0.4)	0	0	0

Abbreviations: AE, adverse event; AZL-M, azilsartan medoxomil; OLM-M, olmesartan medoxomil. [a]The death was due to gastrointestinal hemorrhage and shock. The patient had a medical history of hospital admissions for liver cirrhosis secondary to alcoholism and hepatitis C and was currently abusing ethanol.

cardiovascular events in patients with a high metabolic burden, such as those with obesity.

The greater SBP reduction conferred by AZL-M is unlikely to be due to inadequate dosing of OLM-M. As indicated in the OLM-M product label, doses greater than the maximum approved dose of 40 mg have little additional antihypertensive effect.[14] Furthermore, a recent study by Ojima and colleagues[15] suggests that AZL-M has much slower dissociation from the AT_1 receptor compared with that of OLM-M and may explain in part the greater BP reduction associated with AZL-M.

An important aspect of this trial is the use of ABPM to establish the primary end point. ABPM, because of the frequency of readings and early morning data, provides more reliable predictive data on cardiovascular outcomes than conventional office readings.[16–18] Most studies use office BP as the primary determinate of outcome, while ABPM was used in this trial. This is important since a recent outcome trial that used both office and ABPM values but declared office BP change as the primary end point failed to meet its primary end point, while ABPM data showed clear superiority of one compound over another.[19] In the current trial, the data are congruent with each other and provide the same result as the aforementioned study. One reason for this consistency of result as well as a small placebo effect is probably due to a minimum 24-hour ABPM being mandated prior to study entry, thus excluding patients with white-coat hypertension.

We failed to find any heterogeneity across all subgroups in this study. One exception was the black subgroup, which demonstrated a trend for less BP reduction in all active treatment groups compared with Caucasians, but a trend of greater efficacy with AZL-M 80 mg compared with OLM-M 40 mg. No data provided a meaningful reason as to why this effect was seen and this is being explored in other studies.

CONCLUSIONS

Data from this study suggest that AZL-M 80 mg is more effective in reducing SBP than the highest approved dose of OLM-M, which is considered to be more effective than others in the ARB class.[20,21] Moreover, the data from the current study have been validated internally by consistency of clinic and ABPM measurements. Outcome studies are needed to assess whether these differences in BP efficacy will be borne out in reduction of cardiovascular events.

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