Blood Pressure–Lowering Efficacy of the Fixed-Dose Combination of Azilsartan Medoxomil and Chlorthalidone: A Factorial Study

Domenic Sica, MD;[1] George L. Bakris, MD;[2] William B. White, MD;[3] Michael A. Weber, MD;[4] William C. Cushman, MD;[5] Patrick Huang, PhD;[6] Andrew Roberts, MS;[6] Stuart Kupfer, MD[6]

From the Virginia Commonwealth University, Richmond, VA;[1] the University of Chicago Pritzker School of Medicine, Chicago, IL;[2] the Calhoun Cardiology Center, University of Connecticut School of Medicine, Farmington, CT;[3] the Downstate Medical Center, Brooklyn, NY;[4] the University of Tennessee College of Medicine, Memphis, TN;[5] and the Takeda Global Research and Development Center, Inc, Deerfield, IL[6]

This study compared the efficacy and safety of fixed-dose combinations (FDCs) of the angiotensin II receptor blocker azilsartan medoxomil (AZL-M) and the thiazide-like diuretic chlorthalidone (CLD) with the individual monotherapies in a double-blind factorial study. A total of 1714 patients with clinic systolic blood pressure (SBP) 160 mm Hg to 190 mm Hg inclusive were randomized to AZL-M 0 mg, 20 mg, 40 mg, or 80 mg and/or chlorthalidone 0 mg, 12.5 mg, or 25 mg. The primary efficacy end point was change from baseline to 8 weeks in trough (hour 22–24) SBP by ambulatory blood pressure (BP) monitoring (ABPM). Patients' mean age was 57 years; 47% were men and 20% were black. Baseline trough BP was approximately 165/95 mm Hg and 151/91 mm Hg by clinic and ABPM measurements, respectively. For the pooled AZL-M/CLD 40/25-mg and 80/25-mg FDC groups, SBP reduction by ABPM at trough was 28.9 mm Hg and exceeded AZL-M 80 mg and CLD 25 mg monotherapies by 13.8 mm Hg and 13 mm Hg, respectively ($P<.001$ for both comparisons). Discontinuation rates and elevations in serum creatinine were dose-dependent and occurred more often in the AZL-M/CLD groups. In patients with stage 2 hypertension, treatment with the combination of AZL-M and CLD resulted in substantially greater SBP reduction compared with either agent alone. *J Clin Hypertens (Greenwich).* 2012; 14:284–292. ©2012 Wiley Periodicals, Inc.

Single-drug therapy, even when maximally titrated, is at best only modestly effective in achieving blood pressure (BP) <140/90 mm Hg in patients with hypertension.[1] It is increasingly appreciated that the elusive goal of "normal" BP is achieved only if multidrug therapy is employed.[2] Accordingly, treatment guidelines recommend that initial therapy with 2 drugs, including fixed-dose combinations (FDCs), should be considered for patients whose systolic BP (SBP) or diastolic BP (DBP) is >20 mm Hg or >10 mm Hg above target, respectively.[3,4] The options for multidrug therapy are quite diverse with any of a number of FDCs currently available. Most such combinations include a diuretic or a calcium channel blocker (CCB) given together with either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).[2–6]

To date, nearly all FDCs with either an ACE inhibitor or an ARB with a diuretic have used hydrochlorothiazide (HCTZ) with a maximum dose of 25 mg. These combinations have uniformly lowered BP in a dose-dependent fashion based on the dose of HCTZ, presumably based on the degree to which there is a reduction in extracellular fluid volume.[7–9] However, HCTZ is generally viewed as a moderately potent diuretic, and thus it has inherent limitations on the degree to which it can incrementally lower BP when combined with either an ACE inhibitor or an ARB at conventional doses ≤25 mg/d.[10]

Chlorthalidone (CLD) is a thiazide-like diuretic that is pharmacokinetically and pharmacodynamically different from HCTZ, primarily based on a more extended duration of action.[11] As such, it is more likely to maintain net negative sodium (Na^+) balance and thereby substantially add to the BP-lowering effect of a renin-angiotensin-aldosterone system (RAAS) inhibitor. Azilsartan medoxomil (AZL-M) is a prodrug that is quickly hydrolyzed to the active moiety azilsartan, a potent and highly selective ARB with an elimination half-life of approximately 12 hours. This compound has been proven superior to other ARBs, including valsartan and olmesartan, in its BP-lowering ability.[12–14]

The present study was designed to evaluate both the efficacy and safety of various FDCs of AZL-M and CLD with individual monotherapies in patients with stage 2 hypertension. The primary efficacy analysis of this study was between-drug differences in trough (hour 22–24) SBP, as determined by ambulatory BP monitoring (ABPM).

METHODS

Study Design

This was a phase 3, randomized, double-blind, factorial study comparing the antihypertensive efficacy and

Address for correspondence: Domenic Sica, MD, Division of Nephrology, Department of Medicine and Pharmacology, Chairman Clinical Pharmacology and Hypertension, Virginia Commonwealth University Health System, Richmond, VA
E-mail: dsica@mcvh-vcu.edu

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safety of an FDC containing AZL-M and CLD with each monotherapy. Before randomization, all patients received 2 weeks of single-blind treatment with placebo only. Previously treated patients stopped their antihypertensive medications 1 to 2 weeks before the placebo run-in, resulting in a 3- to 4-week washout of other BP-lowering agents. After the washout/run-in was complete, eligible patients were randomized to 8 weeks of double-blind treatment with AZL-M 20 mg, 40 mg, or 80 mg; CLD 12.5 or 25 mg; or 1 of the 6 combinations of these doses (AZL-M/CLD: 20/12.5 mg, 40/12.5 mg, 80/12.5 mg, 20/25 mg, 40/25 mg, and 80/25 mg). Treatment assignment was stratified by race (ie, black or non-black). Ambulatory BP was recorded at baseline and weeks 4 and 8, and clinic (seated, trough) BP was measured at each of the several study visits.

Men and women who were 18 years and older were recruited from 175 investigative sites in the United States, Latin America, Europe, and Russia. Before initiation of any study procedures, each patient was informed of the study details and signed an informed consent form approved by regional or local institutional review boards. At randomization, each patient was required to have a clinic SBP $\geq$160 mm Hg and $\leq$190 mm Hg. Exclusion criteria included known or suspected secondary hypertension or severe diastolic hypertension (>119 mm Hg); advanced renal disease (estimated glomerular filtration rate [GFR] <30 mL/min/1.73 m^2); clinically relevant or unstable cardiovascular diseases present within 6 months of enrollment; poorly controlled diabetes (glycated hemoglobin >8.0%); clinically significant hepatic abnormalities; or abnormal potassium (K^+) levels (ie, above or below normal reference range). A baseline ABPM reading of insufficient quality, poor compliance during the placebo run-in period, and night-shift work were also exclusionary. In addition, pregnant or nursing women and women of childbearing potential not using medically approved means of contraception were excluded.

BP Assessments

Ambulatory BP was recorded with a portable, automated device (Model 90207; Spacelabs, Inc, Issaquah, WA)[15] during the 24 hours before randomization and during the 24 hours after dose administration at weeks 4 and 8 of the double-blind treatment period. For patients who discontinued prematurely, a final ABPM was attempted if the patient had received at least 4 weeks of double-blind treatment. Ambulatory 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 for the ABPM readings included a starting time of 8 AM $\pm$ 2 hours, a monitoring period of at least 24 hours, record of at least 80% of the expected BP readings, no more than 2 nonconsecutive hours with <1 valid BP reading, and no consecutive hours with <1 valid BP reading. If a baseline or week 8 recording was unsuccessful, the treatment period could be extended and the ABPM repeated within 4 to 5 days. If the repeat recording failed, the ambulatory BP data were considered nonevaluable. A repeat attempt was not made for unsuccessful week 4 recordings.

Clinic BP was measured at baseline and each postrandomization visit (weeks 1, 2, 4, 6, and 8) using a manual, mercury-free device with an indicator display to assist in applying a 2-mm Hg per second deflation rate (Greenlight 300 sphygmomanometer; Accoson, Harlow, UK).[16] Three clinic BP measurements were obtained at 2-minute intervals approximately 24 hours after the previous dose of study medication, and after the patient had been seated for 5 minutes. In addition, a single BP measurement was obtained after the patient remained standing for 2 minutes to evaluate orthostatic BP change.

Safety Assessments

Safety monitoring procedures included recording of adverse events, clinical laboratory test results, vital sign measurements, electrocardiography (ECG), and physical examination findings. 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. In addition, investigators were instructed to report serum creatinine elevations $\geq$30% from baseline and >upper limit of normal (ULN) as an adverse event of special interest, and patients were to be followed after study drug discontinuation until the elevations reversed to $\leq$0.2 mg/dL above baseline or screening values. Patients with creatinine values $\geq$50% from baseline and >ULN were to be considered for discontinuation if elevations were confirmed by a repeat test within 5 to 7 days. Safety laboratory parameters were evaluated at multiple visits by a centralized laboratory (Covance, Indianapolis, IN). Key laboratory parameters included those related to renal function (serum creatinine, urinary albumin to creatinine ratio), electrolyte homeostasis (serum potassium, sodium), and serum uric acid.

Statistics

End Points. The primary end point was the change in trough SBP by ABPM at week 8; the trough period of the ABPM recording was defined as hours 22 to 24 after dosing. The key secondary end points were (1) change in trough SBP by ABPM in black patients, and (2) change in clinic SBP in all patients. Other secondary end points included the change from baseline in trough DBP by ABPM and clinic DBP. The percentage of patients who achieved BP targets (SBP <140 mm Hg, DBP <90 mm Hg, or both) was also evaluated.

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. All statistical tests were 2-sided and results were presented with 95% confidence intervals (CIs) and *P* values at the 5% significance level. The primary analysis involved comparison of pooled results from the treatment arms receiving the 40/25-mg and 80/25-mg doses of the FDC compared with the highest doses of each monotherapy (ie, AZL-M 80 mg and CLD 25 mg). Cell-by-cell analyses that compared each dose of the FDC with its individual monotherapy components were also completed. Analyses were based on the last-observation-carried-forward. 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. Subgroup analyses were performed for the primary end point by age (<65, ≥65 years), sex, race (black, white, other), baseline trough SBP by ABPM (<median, ≥median), body mass index (BMI) (<30, ≥30 kg/m^2), renal function (estimated GFR ≥90 [normal], ≥60 to <90 [mild impairment], ≥30 to <60 mL/min/1.73 m^2 [moderate impairment]),[17] and diabetes. For the above subgroups, post hoc analyses were performed on the primary end point and included the subgroup as a fixed effect to the ANCOVA along with the treatment by subgroup interaction.

Sample Size. A sample size of 1650 patients (150 per arm) was determined as sufficient to achieve at least 90% power to detect a difference of 5 mm Hg between the FDC (pool of the 40/25-mg and 80/25-mg doses) and the highest doses of each monotherapy for the primary end point, assuming a 2-sided significance level of 5%, a standard deviation of 14 mm Hg, and a 15% dropout rate.

RESULTS

Patient Disposition and Demographics

A total of 5145 patients were screened, and 3607 patients were enrolled in the placebo run-in period. Of these patients, 1714 met the entry criteria and were randomized to one of the 11 active treatments (147 to 162 per group); 1470 (85.7%) patients completed the study as planned. There were fewer discontinuations during treatment with monotherapy or lower doses of the FDC (ie, 20/12.5 mg, 20/25 mg, and 40/12.5 mg) compared with higher doses of the FDC (40/25 mg, 80/12.5 mg, and 80/25 mg). The most common reasons for discontinuation were adverse events, voluntary withdrawal, and lack of efficacy (Figure 1).

In the overall study population, the mean age was 57 years, and there was a similar proportion of men and women. Approximately 70% of patients were white and 20% were black; most of the 8% of patients who reported being American Indian were enrolled at Latin American sites. Fourteen percent of patients had type 1 or 2 diabetes. Across treatment groups, the range of mean baseline trough BP by ABPM was 149 to 154 mm Hg/89 to 92 mm Hg, and the range of mean trough clinic BP was 163 to 166 mm Hg/94 to 96 mm Hg (Table I).

SBP by ABPM and Clinic Measurement

At week 8, the highest doses of AZL-M/CLD (40/25 mg and 80/25 mg) produced clinically and statistically significantly greater reductions in trough SBP by both ABPM (primary end point) and clinic measurement (key secondary end point) compared with the highest doses of AZL-M and CLD monotherapy (Table II). Similarly, each of the 6 individual AZL-M/CLD doses led to significantly greater reductions in both clinic and ABPM measures of trough SBP compared with their respective AZL-M and CLD components (Figure 2). For the ABPM results, greater reductions were also seen with AZL-M/CLD at each hour of the ambulatory recording (Figure 3). Reductions in trough SBP by ABPM observed with each dose of AZL-M/CLD were nearly additive relative to their monotherapy components. For both the ABPM and clinic measures, reductions in trough SBP were generally dose-related, although the 80/25-mg dose of AZL-M/CLD did not afford consistent incremental reduction compared with the 40/25-mg dose.

Diastolic BP

As with the systolic results, there were significantly greater reductions in trough DBP with each dose of AZL-M/CLD compared with the respective monotherapy components (Figure 2). Consistently greater diastolic reductions were maintained with AZL-M/CLD throughout the 24-hour recording interval (data not shown).

Achievement of BP Targets

Each of the 6 AZL-M/CLD doses led to a significantly higher proportion of patients who achieved BP targets compared with their respective AZL-M and CLD components. The proportion of patients who achieved both a target SBP <140 mm Hg and a target DBP <90 mm Hg ranged between 70% and 85% in the FDC groups, between 30% and 52% with AZL-M monotherapy, and between 34% and 51% with CLD monotherapy (Figure 4).

Results in Black Patients

BP reductions in black patients who received AZL-M/CLD were similar to those observed in the total study population, although there was a trend for less response to AZL-M monotherapy and greater response to CLD monotherapy in black patients (Table II). Overall, the antihypertensive response observed across all treatment groups for the primary end point was not significantly dependent on race (*P*=.132).

Other Subgroups

In other subgroups, there also were similarly greater reductions in SBP and DBP with AZL-M/CLD vs the

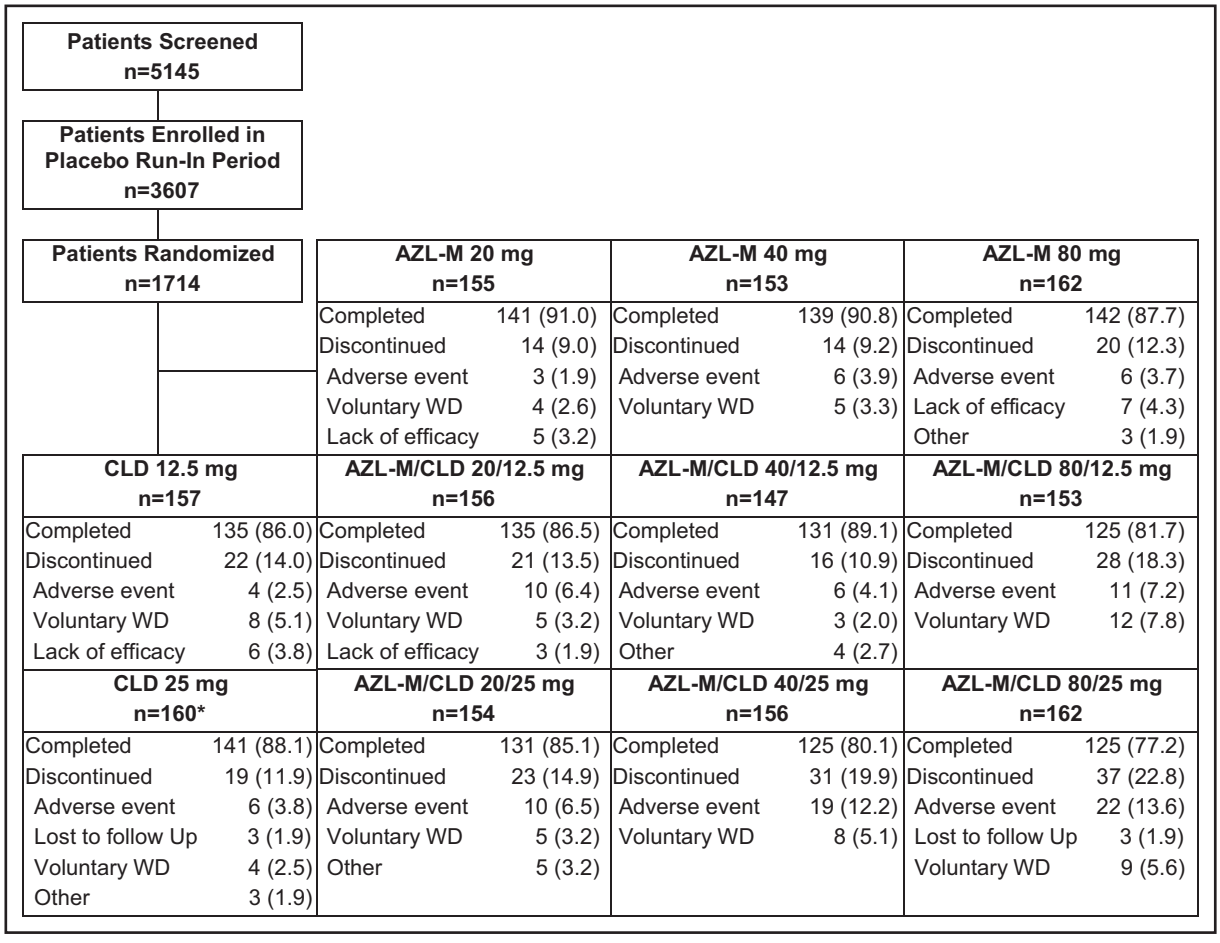

FIGURE 1. Patient disposition by treatment group. Data are expressed as No. (%). AZL-M indicates azilsartan medoxomil; WD, withdrawal; CLD, chlorthalidone. Reasons for discontinuation by >2 patients in each group are listed. *Includes 1 patient who received study drug but was not randomized.

monotherapy components (data not shown). There was no evidence that the antihypertensive effect observed across treatment groups for the primary end point was dependent on age, sex, BMI, renal function, or diabetes status ($P>.10$). Reduction in SBP was greater in patients with higher systolic pressures at baseline in all treatment groups. DBP reductions tended to be greater among patients younger than 65 years compared with those 65 and older; however, the latter subgroup also had a lower average DBP at baseline.

Safety Findings

Adverse events, including serum creatinine increases and dizziness, were reported more frequently among patients who received higher doses of AZL-M/CLD compared with CLD alone. However, reports of hypotension were infrequent in the AZL-M/CLD groups (0.6%–3.1%) and there were few reports of syncope (3 AZL-M/CLD-treated patients), none of which were considered serious by the investigator. The percentage of patients who had consecutive creatinine elevations was low in the monotherapy groups (<1% patient/group) and dose-related in the AZL-M/CLD groups (0.6–5%). Among individual patients, creatinine elevations were typically transient or nonprogressive, associated with relatively large BP reductions and reversible after drug discontinuation. Shifts from normal to below-normal serum potassium levels were infrequent in the AZL-M monotherapy and AZL-M/CLD groups, but were common with CLD monotherapy (Table III). The mean changes in potassium were consistent with these shifts (0.08 mmol/L, −0.42 mmol/L, and −0.08 mmol/L for AZL-M, CLD, and AZL-M/CLD, respectively).

DISCUSSION

A considerable legacy, dating to the 1950s, exists for FDC therapy. The rationale for this approach has remained constant since that time in that 2 drugs, each working at a different site to block different effector pathways, yield greater BP reductions in tandem than can be achieved with the highest dose of any single agent. In addition, for some combinations, 1 of the 2 drugs in an FDC may check counter-regulatory system

TABLE I. Baseline Characteristics of Randomized Patients

		AZL-M 20 mg (n=155)	AZL-M 40 mg (n=153)	AZL-M 80 mg (n=162)
Age, y		57±11.0	58±10.3	57±10.9
Male/female, %		44/56	56/44	48/52
Race, No. (%)				
American Indian		11 (7)	13 (9)	14 (9)
Black		31 (20)	35 (23)	35 (22)
White		113 (73)	105 (69)	111 (69)
BMI, kg/m^2		31±5.2	31±5.9	31±6.3
Trough BP, mm Hg				
Clinic		163/95	164/95	164/95
ABPM		151/91	154/92	151/91
	CLD 12.5 mg (n=157)	AZL-M/CLD 20/12.5 mg (n=156)	AZL-M/CLD 40/12.5 mg (n=147)	AZL-M/CLD 80/12.5 mg (n=153)
Age, y	57±11.3	58±10.6	56±10.5	56±11.2
Male/female, %	53/47	45/55	48/52	46/54
Race, No. (%)				
American Indian	14 (9)	9 (6)	13 (9)	12 (8)
Black	31 (20)	34 (22)	29 (20)	26 (17)
White	111 (71)	111 (71)	102 (69)	114 (75)
BMI, kg/m^2	31±5.9	32±5.7	32±6.6	31±5.8
Trough BP, mm Hg				
Clinic	164/96	165/95	165/96	165/94
ABPM	152/92	151/90	153/91	149/89
	CLD 25 mg (n=159)	AZL-M/CLD 20/25 mg (n=154)	AZL-M/CLD 40/25 mg (n=156)	AZL-M/CLD 80/25 mg (n=162)
Age, y	56±10.0	57±11.1	57±11.1	58±11.0
Male/female, %	43/57	50/50	46/54	38/62
Race, No. (%)				
American Indian	14 (9)	13 (8)	13 (8)	16 (10)
Black	29 (18)	28 (18)	30 (19)	34 (21)
White	111 (70)	112 (73)	111 (71)	109 (67)
BMI, kg/m^2	31±5.8	31±5.7	32±6.0	32±6.3
Trough BP, mm Hg				
Clinic	166/96	165/96	164/94	164/94
ABPM	151/91	151/91	149/89	153/91

Abbreviations: ABPM, ambulatory blood pressure monitoring; AZL-M, azilsartan medoxomil; BP, blood pressure; CLD, chlorthalidone. Age and body mass index (BMI) data are expressed as mean±standard deviation. Three most common race categories are listed; race categories are not mutually exclusive. Other percentages may not add to 100% due to rounding.

activity triggered by the other and/or lessen side effects.[1]

In the present study, there were greater SBP and DBP reductions throughout the 24-hour interval, as well as greater target BP achievement, with all 6 doses of AZL-M/CLD relative to their respective monotherapy components. Reductions in trough SBP by ABPM observed with each FDC were nearly additive relative to their monotherapy components. The reductions in BP were seen with both ABPM and clinic measurement. These BP changes are illustrated in Figure 3, which shows changes in SBP during the 24 hours after dosing at week 8 for the maximally effective FDC, AZL-M/CLD 40/25 mg, and its monotherapy components AZL-M 40 mg and CLD 25 mg. Treatment with AZL-M/CLD resulted in a similar magnitude of BP reduction in black patients compared with the overall population, even though black patients are often less responsive to RAAS blockade. In the monotherapy groups, response in black patients tended to be greater with CLD and attenuated with AZL-M.

Even with substantial BP differences between the FDCs and monotherapy treatment groups, the frequency of treatment-emergent adverse events reported with the lower doses of AZL-M/CLD (55–59%) was similar to that with CLD monotherapy (53–58%), although fewer adverse events were reported with AZL-M monotherapy (43–49%). The incidence of adverse events was dose-related, with a higher frequency of events reported with the 40/25-mg (68%) and 80/25-mg (62%) doses of the FDC. Although the factorial design of this study allowed for the most

TABLE II. Trough SBP by ABPM and Trough Clinic SBP: Highest FDC Doses vs Highest Doses of AZL-M and CLD Monotherapy

	Trough SBP by ABPM, mm Hg			Clinic SBP, mm Hg		
	AZL-M (80 mg)	CLD (25 mg)	AZL-M/CLD (40/25+80/25 mg)	AZL-M (80 mg)	CLD (25 mg)	AZL-M/CLD (40/25+80/25 mg)
All patients,						
No.	127	134	228	162	156	313
Baseline	151.1±1.45	151.2±1.41	152.2±1.08	163.9±0.80	166.1±0.82	164.3±0.58
Change at wk 8	−15.1±1.19	−15.9±1.16	−28.9±0.89	−24.2±1.23	−27.1±1.25	−39.8±0.88
Difference	−13.8[a] (−16.7 to −10.9)	−13.0[b] (−15.8 to −10.1)	–	−15.7[a] (−18.6 to −12.7)	−12.7[b] (−15.7 to −9.7)	–
Black patients,						
No.	28	22	40	35	29	63
Baseline	153.9±3.00	151.4±3.38	154.2±2.51	163.6±1.75	165.1±1.92	165.6±1.31
Change at wk 8	−9.9±2.97	−23.4±3.36	−28.2±2.49	−19.7±2.71	−31.3±2.98	−40.2±2.02
Difference	−18.2[a] (−25.9 to −10.6)	−4.8 (−13.0 to 3.5)	–	−20.5[a] (−27.1 to −13.8)	−8.9[b] (−16.0 to −1.8)	

Abbreviations: ABPM, ambulatory blood pressure monitoring; FDC, fixed-dose combination; SBP, systolic blood pressure. Blood pressure data are expressed as mm Hg; baseline values and change from baseline values as least-square mean±standard error of the mean; and differences as least-square mean (95% confidence interval) of azilsartan medoxomil/chlorthalidone (AZL-M/CLD) vs AZL-M or CLD. [a]Statistically significantly greater reduction than AZL-M 80 mg ($P<.05$). [b]Statistically significantly greater reduction than CLD 25 mg ($P<.05$).

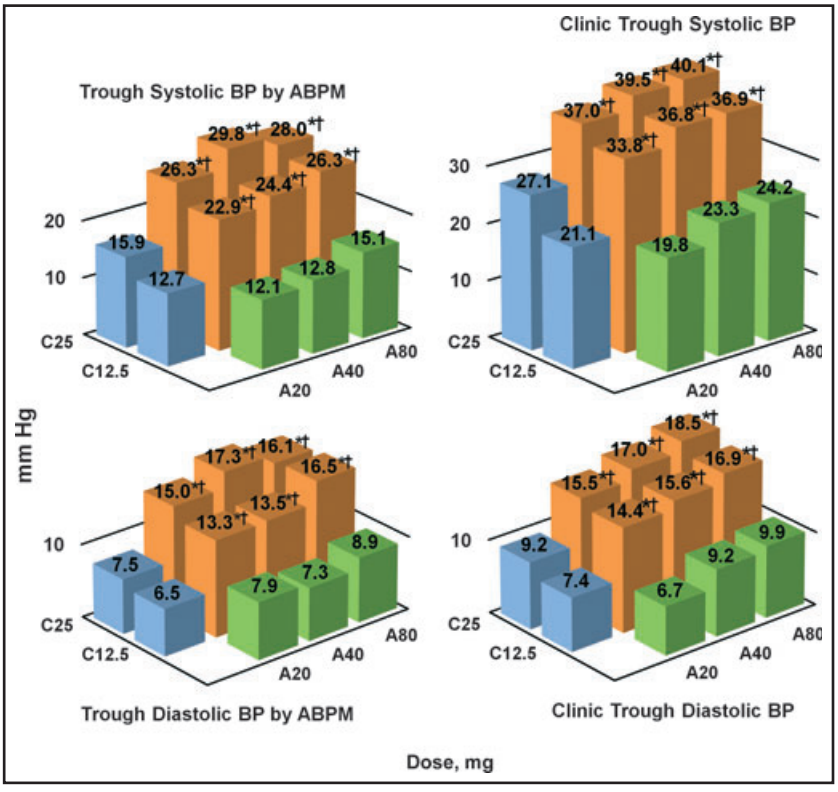

FIGURE 2. Trough blood pressure (BP) reductions at week 8 (last observation carried forward) by treatment group. Data are presented as least-square mean change from baseline. *Statistically significantly greater reduction than azilsartan medoxomil (A) component ($P<.05$). †Statistically significantly greater reduction than chlorthalidone (C) component ($P<.05$). ABPM indicates ambulatory BP monitoring.

accurate comparison of the true BP effects of each treatment, it is contrary to usual clinical practice, where titration to higher doses is reserved for patients who have not achieved BP targets at lower doses. Consequently, direct randomization to higher doses of AZL-M/CLD may have resulted in a greater occur-

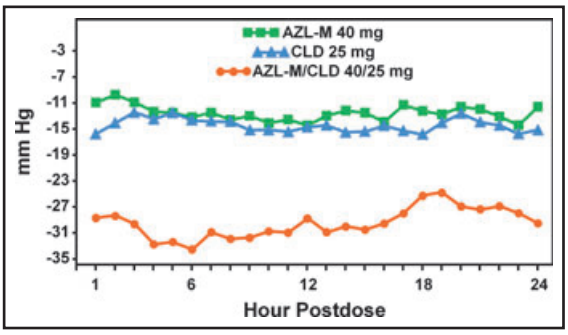

FIGURE 3. Change from baseline in systolic blood pressure (BP) by hour at week 8. Data for the maximally effective dose of the azilsartan medoxomil/chlorthalidone (AZL-M/CLD) fixed-dose combination (40/25 mg) and its individual components (AZL-M 40 mg and CLD 25 mg) are shown.

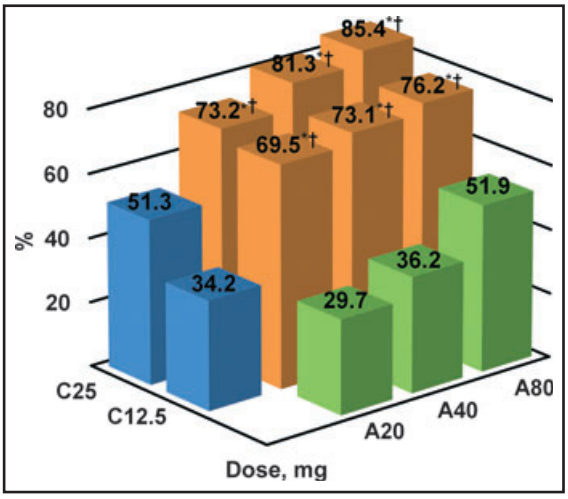

FIGURE 4. Target blood pressure (BP) achievement by treatment group. Target BP was defined as systolic BP <140 mm Hg and diastolic BP <90 mm Hg. *Statistically significantly higher proportion of responders compared with the azilsartan medoxomil (A) component ($P<.05$). †Statistically significantly higher proportion of responders than the chlorthalidone (C) component ($P<.05$).

rence of mechanism-based side effects, including dizziness and elevations of serum creatinine. The fact that serum creatinine values were elevated more frequently with the FDC than with AZL-M monotherapy also suggests that the diuretic effect of CLD contributed to these increases, as the renal hemodynamic effects of an ARB are known to be volume-dependent.[18] While creatinine elevations were more frequent in the AZL-M/CLD groups, they were nonprogressive or reversible after treatment discontinuation. In addition, hypokalemia, which may result from diuretic-induced potassium wasting, was observed less frequently in the FDC groups than with CLD monotherapy, suggesting that inhibition of RAAS activity with AZL-M counteracts this effect.

In the past 30 years, a plethora of FDCs have reached the market, with the majority in the United States containing HCTZ;[19] alternatively, there are but 2 FDCs containing the thiazide-type diuretic CLD (atenolol/CLD [Tenoretic; AstraZeneca Pharmaceuticals, Wilmington, DE], clonidine/CLD [Combipres; Boehringer-Ingelheim, Ridgefield, CT) despite the fact that CLD has been the most extensively studied diuretic with proven cardiovascular outcomes,[20–22] particularly when compared with contemporary doses of HCTZ.[23] CLD is distinguished from HCTZ in having a long half-life (40–60 hours) and a large volume of distribution owing to its heavy partitioning into red blood cells. This latter feature creates a depot for CLD, allowing for a slow streaming effect (red cell → plasma) with subsequent gradual elimination from the plasma compartment occurring by tubular secretion.[24] In contrast, HCTZ has a much shorter half-life with a wider variation, from 3.2 to 13.1 hours.[25] This plasma half-life difference can be expected to correlate with a more extended effect of CLD on diuresis and BP reduction.

The incremental reduction in BP with the FDC containing 25 mg of CLD was appreciably greater than what has previously been seen with an FDC containing 25 mg of HCTZ and the ARB olmesartan. For example, treatment with olmesartan/HCTZ 40/25 mg reduced seated clinic SBP and DBP an additional 7 mm Hg and 5 mm Hg, respectively, compared with monotherapy with olmesartan 40 mg.[26] In the present study, the incremental benefit for clinic seated SBP and DBP reduction with CLD 25 mg, in addition to either 40 mg or 80 mg of AZL-M was 16 mm Hg and 8 mm Hg at trough. However, such cross-study comparisons may not accurately reflect the BP differences if a direct comparison of HCTZ with chlorthalidone (in addition to an ARB) were being made. Although the mechanistic basis for this significant additional reduction in BP with the addition of CLD to AZL-M was not explored in these studies, it is most likely related to a more prolonged diuretic effect of CLD. This differing degree of diuretic additivity for CLD is further supported by the HCTZ dose-escalation studies of Lacourcière and colleagues,[8] which showed an additional 4.4-mm Hg drop in mean ambulatory daytime SBP when a 25-mg dose of HCTZ, given together with losartan, was increased to 37.5 mg/d. Presumably, the higher dose of HCTZ used in this study provided a longer period of time during which a diuresis might occur and therein enhanced the BP-lowering effect of losartan.

CONCLUSIONS

These are the first studies using CLD together with an ARB in an FDC. The reduction in BP with this FDC is significantly greater than what has been observed with a similar dose of HCTZ given in an FDC with any of a number of ARBs.[27] The availability of an FDC with

TABLE III. Safety Findings by Treatment Group

		AZL-M 20 mg (n=155)	AZL-M 40 mg (n=153)	AZL-M 80 mg (n=162)
Total AEs		70 (45.2)	75 (49.0)	70 (43.2)
Serious AE		2 (1.3)	2 (1.3)	3 (1.9)
Common AEs				
SCr increased		4 (2.6)	5 (3.3)	6 (3.7)
Dizziness		2 (1.3)	7 (4.6)	6 (3.7)
Headache		13 (8.4)	11 (7.2)	12 (7.4)
Select laboratory value shifts				
Normal to ↑ SCr		2 (1.3)	7 (4.7)	4 (2.5)
Normal to ↓ K^+		1 (0.7)	1 (0.7)	2 (1.3)
Normal to ↑ K^+		1 (0.7)	2 (1.3)	0 (0.0)
Normal to ↓ Na^+		0 (0.0)	0 (0.0)	1 (0.6)
Normal to ↑ UA		4 (2.7)	14 (9.7)	6 (4.1)
	CLD 12.5 mg (n=156)	AZL-M/CLD 20/12.5 mg (n=156)	AZL-M/CLD 40/12.5 mg (n=146)	AZL-M/CLD 80/12.5 mg (n=153)
Total AEs	82 (52.6)	92 (59.0)	83 (56.8)	84 (54.9)
Serious AE	0 (0.0)	3 (1.9)	1 (0.7)	2 (1.3)
Common AEs				
SCr increased	5 (3.2)	15 (9.6)	17 (11.6)	19 (12.4)
Dizziness	6 (3.8)	12 (7.7)	20 (13.7)	19 (12.4)
Headache	19 (12.2)	8 (5.1)	1 (0.7)	11 (7.2)
Select laboratory value shifts				
Normal to ↑ SCr	2 (1.3)	7 (4.6)	9 (6.4)	9 (6.1)
Normal to ↓ K^+	14 (9.3)	4 (2.6)	1 (0.7)	1 (0.7)
Normal to ↑ K^+	1 (0.7)	2 (1.3)	0 (0.0)	2 (1.3)
Normal to ↓ Na^+	1 (0.7)	2 (1.4)	3 (2.2)	2 (1.4)
Normal to ↑ UA	34 (23.9)	32 (21.8)	37 (28.2)	34 (24.3)
	CLD 25 mg (n=160)	AZL-M/CLD 20/25 mg (n=154)	AZL-M/CLD 40/25 mg (n=156)	AZL-M/CLD 80/25 mg (n=161)
Total AEs	92 (57.5)	88 (57.1)	106 (67.9)	100 (62.1)
Serious AE	2 (1.3)	0 (0.0)	2 (1.3)	2 (1.2)
Common AEs				
SCr increased	9 (5.6)	19 (12.3)	29 (18.6)	32 (19.9)
Dizziness	5 (3.1)	17 (11.0)	21 (13.5)	19 (11.8)
Headache	17 (10.6)	12 (7.8)	9 (5.8)	11 (6.8)
Select laboratory value shifts				
Normal to ↑ SCr	8 (5.3)	8 (5.4)	15 (9.9)	18 (11.5)
Normal to ↓ K^+	27 (17.4)	10 (6.5)	4 (2.6)	2 (1.3)
Normal to ↑ K^+	0 (0.0)	0 (0.0)	1 (0.6)	2 (1.3)
Normal to ↓ Na^+	1 (0.7)	0 (0.0)	6 (4.1)	3 (2.1)
Normal to ↑ UA	35 (24.1)	44 (31.2)	52 (35.9)	51 (33.8)

Abbreviations: AZL-M, azilsartan medoxomil; CLD, chlorthalidone. Data are expressed as No. of patients (percentage). Common adverse events (AEs) include those reported by ≥5% patients overall. Laboratory value shifts are changes from within the normal range at baseline to >upper limit of normal (ULN) (↑) or <lower limit of normal (LLN) (↓) at the final visit. Serum creatinine (SCr) (mg/dL), ULN, men = 1.2 (18–50 y), 1.3 (50–70 y), 1.5 (70–80 y), 1.6 (>80 y); women = 1.1 (18–70 y), 1.2 (70–80 y), 1.4 (>80 y). Potassium (K^+) (mEq/L), LLN to ULN = 3.4 to 5.4. Sodium (Na^+) (mEq/L), LLN = 132 (18–59 y), 135 (>59 y). Uric acid (UA) (mg/dL), ULN, men = 8.2 (18–50 y), 8.3 (>50 y); women = 7.2 (18–50 y), 7.5 (>50 y).

an ARB and CLD, capable of reducing BP to this degree, offers the opportunity to reframe the paradigm for the treatment of hypertension when multidrug therapy is necessary.

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