CLINICAL RESEARCH STUDY

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Antihypertensive Efficacy of Hydrochlorothiazide vs Chlorthalidone Combined with Azilsartan Medoxomil

George L. Bakris, MD,[a] Domenic Sica, MD,[b] William B. White, MD,[c] William C. Cushman, MD,[d] Michael A. Weber, MD,[e] Alison Handley, PhD,[f] Eric Song, PhD,[f] Stuart Kupfer, MD[f]

[a]The University of Chicago Medicine, Chicago, Ill; [b]Virginia Commonwealth University, Richmond; [c]University of Connecticut School of Medicine, Farmington; [d]University of Tennessee College of Medicine, Memphis; [e]SUNY Downstate Medical Center, Brooklyn, NY; [f]Takeda Global Research and Development Center, Inc, Deerfield, Ill.

ABSTRACT

BACKGROUND: Chlorthalidone has proven efficacy to reduce cardiovascular morbidity and mortality, yet it is infrequently used in practice. This study provides a direct comparison of chlorthalidone with hydrochlorothiazide, each combined with the angiotensin receptor blocker azilsartan medoxomil, on blood pressure reduction and control rates.

METHODS: This is a randomized, double-blind, titrate-to-target blood pressure trial comparing the single-pill combination of azilsartan medoxomil and chlorthalidone versus co-administration of azilsartan medoxomil and hydrochlorothiazide in participants with stage 2 primary hypertension. After 2 weeks of treatment with azilsartan medoxomil 40 mg alone, all participants also received 12.5 mg of diuretic for 4 weeks (up to week 6) and were titrated to 25 mg for another 4 weeks (up to week 10) if they failed to achieve target blood pressure. The primary end point was change in clinic systolic blood pressure. Target blood pressure was defined as clinic blood pressure <140/90 mm Hg for participants without diabetes or chronic kidney disease or <130/80 mm Hg for participants with diabetes or chronic kidney disease.

RESULTS: The mean age of the 609 participants was 56.4 years, and the mean baseline clinic blood pressure was 164.6/95.4 mm Hg. The primary end point analysis at week 6 demonstrated a greater reduction of clinic systolic blood pressure for the chlorthalidone (−35.1 mm Hg) versus hydrochlorothiazide combination (−29.5 mm Hg) (mean difference, −5.6 mm Hg; 95% confidence interval, −8.3 to −2.9; P <.001). The mean difference in 24-hour ambulatory systolic blood pressure at week 6 was −5.8 mm Hg (95% confidence interval, −8.4 to −3.2; P <.001), favoring the azilsartan medoxomil/chlorthalidone group. The percentage of participants achieving target clinic blood pressure at week 6 was greater for the chlorthalidone versus hydrochlorothiazide combination (64.1% vs 45.9%, P <.001). Drug discontinuations due to adverse events were not statistically significantly different between groups (9.3% vs 7.3%, P = .38), and hypokalemia was uncommon in both groups.

CONCLUSIONS: Chlorthalidone combined with azilsartan medoxomil provides better blood pressure reduction and a higher likelihood of achieving blood pressure control than hydrochlorothiazide combined with azilsartan medoxomil. This benefit occurred without a difference in safety measurements.

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KEYWORDS: Angiotensin receptor blocker; Azilsartan medoxomil; Chlorthalidone; Hypertension

Although blood pressure control rates have improved over the past decade,[1] achievement of blood pressure goals continues to be challenging in clinical practice. A number of inroads to improve hypertension control have occurred with the earlier initiation of combination therapy in the course of disease,[2] as outlined in updated guidelines from around the world.[3-6] The use of combination therapy as an initial approach to treat hypertension has finally gained acceptance worldwide.

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Requests for reprints should be addressed to George Bakris, MD, The University of Chicago Medicine, 5841 S. Maryland Ave MC 1027, Chicago, IL 60637.

E-mail address: gbakris@gmail.com

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Most guidelines suggest thiazide-type diuretics with a blocker of the renin-angiotensin-aldosterone system as an initial therapy to help achieve blood pressure goals. Although the majority of outcome trials documenting cardiovascular event risk reduction in patients with hypertension are with chlorthalidone, hydrochlorothiazide has been the diuretic most commonly prescribed by physicians and included in most diuretic renin-angiotensin-aldosterone system blocker single-pill combinations.[6]

There are many pharmacologic and clinical differences between hydrochlorothiazide and chlorthalidone, as outlined in recent studies.[7,8] In particular, chlorthalidone, including its metabolites, has a longer half-life[8,9] than hydrochlorothiazide and its metabolites. Thus, data using ambulatory blood pressure monitoring demonstrate superior blood pressure control of chlorthalidone over hydrochlorothiazide.[8]

Azilsartan medoxomil is a novel renin-angiotensin-aldosterone system blocker that demonstrates superiority on 24-hour blood pressure control over 2 other angiotensin receptor blockers.[10-12] The current study examines the effects of combining azilsartan medoxomil with hydrochlorothiazide or chlorthalidone on blood pressure reduction, control rates, and safety and tolerability.

CLINICAL SIGNIFICANCE

- Chlorthalidone reduced blood pressure more effectively than hydrochlorothiazide, even when combined with the potent angiotensin receptor blocker azilsartan medoxomil.
- Chlorthalidone-induced kaliuresis was substantially attenuated by azilsartan medoxomil because hypokalemia was uncommon in chlorthalidone-treated patients.
- The relatively greater antihypertensive effect of chlorthalidone compared with hydrochlorothiazide in combination with azilsartan medoxomil was observed in the context of comparable safety and tolerability.

MATERIALS AND METHODS

Study Design

This was a 10-week, randomized, double-blind, double-dummy, titrate-to-target blood pressure study comparing the antihypertensive efficacy and safety of a single-pill combination containing azilsartan medoxomil and chlorthalidone with the co-administration of azilsartan medoxomil and hydrochlorothiazide in participants with primary hypertension (**Figure 1**).

Randomization and Masking

Before randomization, all participants received 2 weeks of single-blind treatment with placebo only. Previously treated participants stopped taking their antihypertensive medications 1 to 2 weeks before the placebo run-in, resulting in a 3- to 4-week washout of other blood pressure-lowering agents. After the washout/run-in was complete, participants were randomized using an interactive voice-activated response system. Eligible participants were randomized and initially received 2 weeks of single-blind treatment with azilsartan medoxomil 40 mg once per day. Participants were instructed to dose their study medication once daily in the morning with or without food. At the end of 2 weeks, participants received their randomized, double-blind, double-dummy treatment for 8 weeks: azilsartan medoxomil/chlorthalidone 40/12.5 mg→ 40/25 mg titration strategy or azilsartan medoxomil + hydrochlorothiazide 40/12.5 mg→ 40/25 mg titration strategy. At the end of week 6, investigators were instructed to titrate the study drug from the initial to the higher dose for participants who had not achieved target blood pressure; otherwise, participants continued their initial dose of double-blind treatment. The double-dummy process and the interactive voice–activated response system were used throughout the entire study to ensure that randomized treatment was accurately assigned and that all patients took the same number of identically appearing pills (1 tablet and 1 capsule) at each dosing interval.

Target blood pressure was defined as mean trough, sitting, clinic blood pressure $<$140/90 mm Hg for participants without diabetes or chronic kidney disease or $<$130/80 mm Hg for participants with diabetes or chronic kidney disease. Randomization was stratified by race (ie, black or not black). Clinic, seated blood pressure was measured at each study visit, and ambulatory blood pressure was recorded at baseline, week 6, and week 10.

Study Participants

Inclusion Criteria. Participants aged $\geq$18 years with primary hypertension were recruited from 66 investigative sites in the United States and Russia. Before initiation of any study procedures, each participant was informed of the study details and signed an informed consent form approved by regional institutional review boards. At randomization, each participant was required to have a clinic, seated systolic blood pressure $\geq$160 and $\leq$190 mm Hg (stage 2 hypertension).

Exclusion Criteria. These included known or suspected secondary hypertension or severe diastolic hypertension ($>$119 mm Hg); severe renal impairment (estimated glomerular filtration rate $<$30 mL/min/1.73 m^2); known or suspected renal artery stenosis; clinically relevant or unstable cardiovascular diseases; poorly controlled diabetes (hemoglobin A1c $>$8.0%); clinically significant hepatic abnormalities; and abnormal potassium levels (ie, above or below normal range). In addition, a 24-hour ambulatory blood pressure at baseline of insufficient quality, poor adherence during the placebo run-in period, and night-shift work also were exclusionary. All pregnant or nursing women and those of childbearing potential not using medically ap-

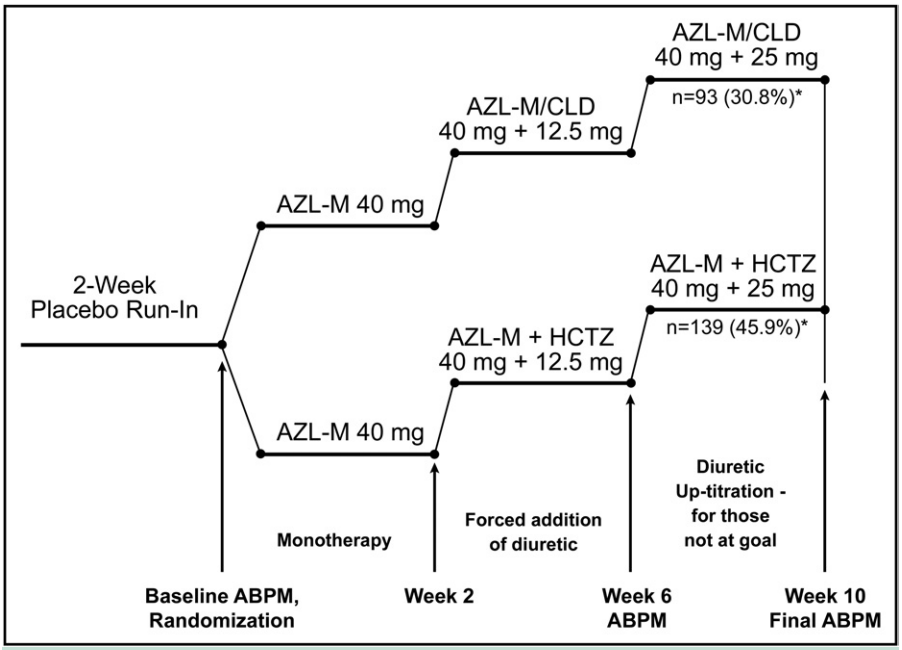

Figure 1 Study design. All participants received 40 mg AZL-M for 2 weeks before initiating AZL-M/CLD or AZL-M + HCTZ with a low-dose (12.5 mg) diuretic; the diuretic dose was to be up-titrated to 25 mg at week 6 if target blood pressure had not been achieved. *The number (percentage) of participants whose diuretic dose was up-titrated from 12.5 to 25 mg at week 6. ABPM = ambulatory blood pressure monitoring; AZL-M = azilsartan medoxomil; AZL-M/CLD = azilsartan medoxomil/chlorthalidone single-pill combination; AZL-M + HCTZ = azilsartan medoxomil + hydrochlorothiazide co-administered.

proved means of contraception also were excluded. Concomitant use of other antihypertensive agents or medications known to affect blood pressure was not permitted.

Blood Pressure Assessment

Clinic blood pressure was measured at baseline and each post-randomization visit (weeks 2, 4, 6, 8, and 10) with a nonautomated, mercury-free sphygmomanometer (Greenlight 300; Accoson, Harlow, UK). Three clinic blood pressure measurements were obtained at 2-minute intervals approximately 24 hours after the previous dose of study medication and after participants were seated for 5 minutes; results of the 3 measurements were averaged. For assessment of orthostatic hypotension, a single blood pressure measurement was obtained after the participant remained standing for 2 minutes.

Twenty-four-hour ambulatory blood pressure monitoring was recorded with a portable, automated device (Model 90207; Spacelabs, Inc, Issaquah, Wash) during the 24 hours before randomization, at the intermediate week 6 visit, and after the final dose of study drug at week 10. For participants who discontinued prematurely, a final ambulatory blood pressure monitoring was attempted if the participant received at least 4 weeks of double-blind treatment. Ambulatory blood pressure monitoring was initiated immediately after study drug administration in the clinic and 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 ambulatory blood pressure monitoring readings included a starting time of 8 AM ± 2 hours, a monitoring period of at least 24 hours, record of at least 80% of the expected blood pressure readings, no more than 2 nonconsecutive hours with <1 valid blood pressure reading, and no consecutive hours with <1 valid blood pressure reading. If a recording was unsuccessful at baseline or week 10, the treatment period could have been extended and the ambulatory blood pressure monitoring could have been repeated within 4 to 5 days. If the repeat recording failed, the ambulatory blood pressure data were considered nonevaluable.

Safety Assessments

Safety monitoring procedures included recording of adverse events, clinical laboratory test results, vital sign measurements, electrocardiogram findings, and physical examination findings. At each visit, the investigator assessed whether the participant had experienced any adverse events, and the participant could report events spontaneously throughout the study. Each event was categorized as nonserious or serious and according to whether or not it resulted in discontinuation of treatment. Safety laboratory parameters were evaluated at each visit, with key laboratory parameters including those related to renal function (serum creatinine, blood urea nitrogen, and urinary albumin-to-

creatinine ratio), electrolyte homeostasis (serum potassium, sodium, chloride, calcium, and magnesium), and metabolic function (serum uric acid, glucose, and lipids). In addition, investigators were instructed to report any serum creatinine elevation, ≥30% from baseline and greater than the upper limit of normal, as an adverse event of special interest. Participants with creatinine values elevated ≥50% from baseline and greater than the upper limit of normal were to be considered for discontinuation if confirmed by a repeat test within 5 to 7 days.

Adherence Assessment

Because the trial design was double-blind, double-dummy, all participants were dispensed the same number of identically appearing pills (1 tablet and 1 capsule) at each dosing interval throughout the trial. Participants were required to return their study medication at each clinic visit, and pill counts were performed to document appropriate adherence, which was defined as taking 80% to 120% of the dispensed pills.

Statistics

End Points. The primary end point was change in trough, seated clinic systolic blood pressure at weeks 6 and 10. The dual time points were selected because they represent the effect before and after the optional titration at week 6. Secondary end points included change from baseline in clinic diastolic blood pressure and 24-hour mean systolic and diastolic blood pressures by ambulatory blood pressure monitoring. Analyses also were performed on night-time (12 AM to 6 AM) and trough (last 2 hours of dosing interval, hours 22-24) readings. The proportion of participants achieving target blood pressure at each visit also was evaluated.

Analysis of End Points. The primary end point was evaluated using an analysis of covariance with treatment as a fixed effect and baseline clinic systolic blood pressure as a covariate. All statistical tests were 2-sided at the 5% significance level, and results were presented with 95% confidence intervals (CIs) and *P* values. A stepwise testing procedure was used to control the type I error rate. The first treatment test was done at week 6. If it was statistically significant at a significance level of 5%, then the treatment comparison at week 10 was performed at the 5% significance level. Secondary clinic and ambulatory blood pressure end points were analyzed with a similar statistical model. Analyses of the clinic blood pressure measurements were based on the last observation carried forward method. A logistic model with treatment as a fixed effect and baseline systolic blood pressure value as a covariate was used in the analysis of responder rates; an odds ratio and its 95% CI were estimated. Exploratory subgroup analyses were performed for each end point by age (<65, ≥65 years), sex, race (black, white, other), baseline clinic systolic blood pressure (less than median, median or greater), body mass index (BMI) (<30, ≥30 kg/m^2), renal function (calculated glomerular filtration rate ≥90 [normal], ≥60 to <90 [mild impairment], ≥30 to <60 mL/min/1.73 m^2 [moderate impairment]), and presence of diabetes. For these subgroups, post hoc analyses were performed on the primary end point at week 6 before titration (when all participants were receiving 12.5 mg of diuretic), using the primary analysis model by including the subgroup as a fixed effect to the analysis of covariance along with the treatment subgroup interaction. Adverse event *P* values were calculated using a 2-sided Fisher exact test without adjustment for multiplicity.

Sample Size. A sample size of 600 randomized participants (300 per group) was determined sufficient to achieve at least 90% power to detect a difference of 4 mm Hg between the azilsartan medoxomil/chlorthalidone group and the azilsartan medoxomil + hydrochlorothiazide group for the primary end point of clinic systolic blood pressure by a 2-sample *t* test, assuming a 2-sided significance level of 5%, a standard deviation of 14 mm Hg, and a 15% dropout rate.

RESULTS

Study Participants

Participants (n = 1652) were screened at 66 sites in the United States and Russia. Of these, 1193 participants (72.2%) entered the single-blind placebo run-in period, and 609 participants (51%) were randomized to treatment at 63 sites; 303 and 306 participants were randomized to the azilsartan medoxomil/chlorthalidone and azilsartan medoxomil + hydrochlorothiazide treatment groups, respectively (**Figure 2**).

Demographics

The demographic and baseline characteristics are summarized in **Table 1**. The mean age was 56.4 years, the percentage of male and female participants was similar, and the percentage of black participants was 13.8% (84). The mean baseline clinic blood pressure at randomization before any active treatment was 164.6/95.4 mm Hg. An analysis found differences in 2 baseline subgroups (**Table 1**). When tested for interactions with primary outcome variables, however, there were no interactions.

Primary Outcome

The primary end point of change in clinic systolic blood pressure before titration at week 6 demonstrated a mean difference of −5.6 mm Hg (95% CI, −8.3 to −2.9; *P* <.001) (**Figure 3A**) in favor of azilsartan medoxomil/chlorthalidone. After 6 weeks of treatment, participants with uncontrolled blood pressure were to be titrated to a higher dose of diuretic (**Figure 1**). Fewer participants in the azilsartan medoxomil/chlorthalidone group (93 [30.8%]) were titrated than those in the azilsartan medoxomil + hydrochlorothiazide group (139 [45.9%]) (*P* <.001). Nevertheless, at the end of

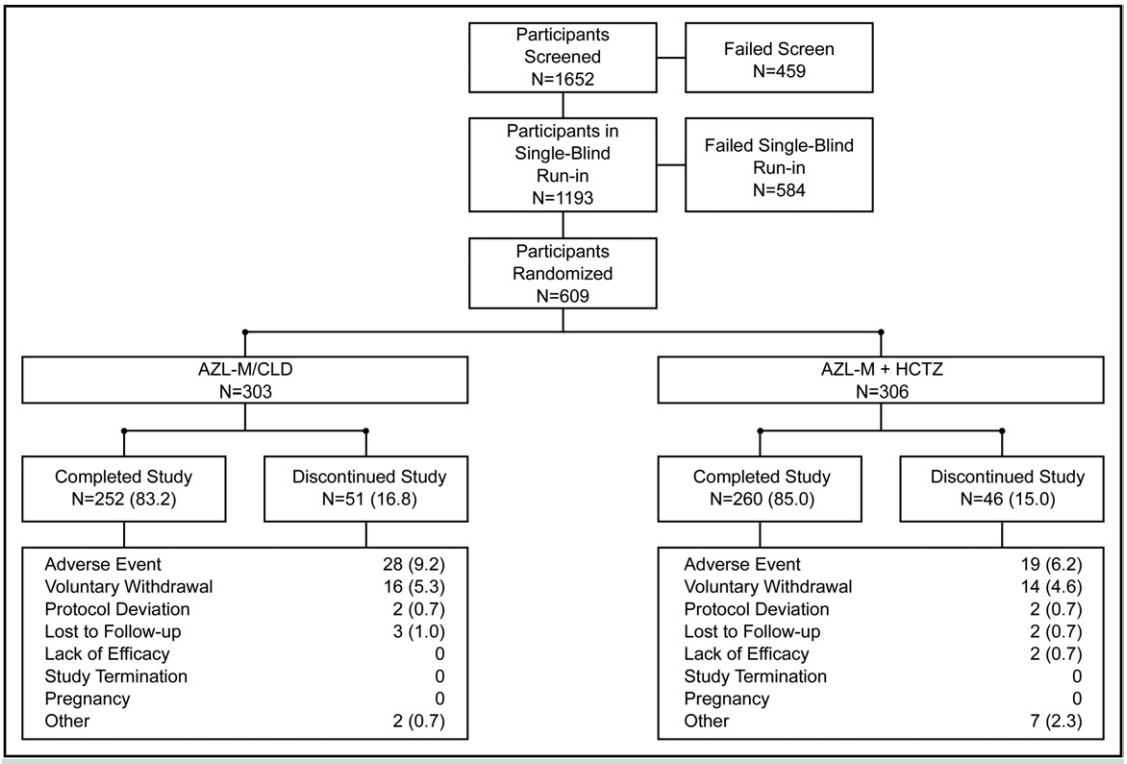

Figure 2 Disposition of participants. Data are n (%). AZL-M/CLD = azilsartan medoxomil/chlorthalidone single-pill combination; AZL-M + HCTZ = azilsartan medoxomil + hydrochlorothiazide co-administered.

week 10, a greater mean (difference, 95% CI) systolic blood pressure reduction was maintained in the azilsartan medoxomil/chlorthalidone group compared with the azilsartan medoxomil + hydrochlorothiazide group (−5.0 mm Hg; 95% CI, −7.5 to −2.5; $P < .001$) (**Figure 3A**).

Secondary Outcomes

Azilsartan medoxomil/chlorthalidone reduced 24-hour mean systolic blood pressure to a significantly greater extent than azilsartan medoxomil + hydrochlorothiazide at the end of weeks 6 and 10 (**Figure 3B**). Likewise, for both clinic and 24-hour mean diastolic blood pressure, greater blood pressure reduction also was observed in the azilsartan medoxomil/chlorthalidone group compared with the azilsartan medoxomil + hydrochlorothiazide group at both study points (**Table 2**). An analysis of nocturnal systolic blood pressures between groups did not show differences; however, there were distinct differences in early morning, trough systolic blood pressures between groups (**Figure 3C**).

Azilsartan medoxomil/chlorthalidone treatment resulted in a greater proportion of participants achieving target blood pressure at the end of week 6 compared with azilsartan medoxomil + hydrochlorothiazide (189 [64.1%] vs 134 [45.9%], $P < .001$) (**Table 3**). Despite the fact that more participants were titrated to the higher diuretic dose at week 6 in the azilsartan medoxomil + hydrochlorothiazide group, a greater proportion of participants achieved target blood pressure at the end of week 10 in the azilsartan medoxomil/chlorthalidone group (211 [71.5%] vs 182 [62.3%], $P = .013$).

For nearly all the analyzed subgroups, treatment with azilsartan medoxomil/chlorthalidone led to greater decreases in clinic systolic blood pressure compared with azilsartan medoxomil + hydrochlorothiazide at the end of week 6 (**Figure 4**). We further tested for interactions, and there was no statistical evidence ($P > .10$) that response to treatment was dependent on any one of the subgroups of age, sex, race, BMI, renal function, or diabetes. Adherence to medications between groups showed no significant difference (289 [95.7%] for azilsartan medoxomil/chlorthalidone and 294 [97.0%] for azilsartan medoxomil + hydrochlorothiazide; $P = .396$).

Adverse Events

The safety profiles of the azilsartan medoxomil/chlorthalidone and azilsartan medoxomil + hydrochlorothiazide groups were similar and are summarized in **Table 4**. Although the frequencies of total adverse events and drug discontinuations due to adverse events were slightly higher in the azilsartan medoxomil/chlorthalidone group, the differences were not significant (**Table 4**). The most common adverse events accounting for study drug discontinuation were dizziness (3 [1.0%] vs 5 [1.7%]) and increased serum creatinine (12 [4.0%] vs 6 [2.0%]) in the azilsartan medoxomil/chlorthalidone and azilsartan medoxomil + hydro-

Table 1 Demographics and Baseline Characteristics

Characteristic	AZL-M/CLD (N = 303)	AZL-M + HCTZ (N = 306)	*P* Value
Sex, n (%)			.746*
Male	145 (47.9)	151 (49.3)	
Female	158 (52.1)	155 (50.7)	
Age (y), mean (SD)	56.8 ± 10.8	55.9 ± 11.0	.324†
Age categories (y), n (%)			.515*
<45	43 (14.2)	50 (16.3)	
45-64	189 (62.4)	195 (63.7)	
≥65	71 (23.4)	61 (19.9)	
Race, n (%)			.037‡
Caucasian	252 (83.2)	265 (86.6)	
Black or African American	46 (15.2)	38 (12.4)	
American Indian or Alaska Native	6 (2.0)	1 (0.3)	
Asian	3 (1.0)	2 (0.7)	
Native Hawaiian or Other Pacific Islander	1 (0.3)	0	
Multiple	5 (1.7)	0	
Weight (kg), mean (SD)	87.6 ± 19.2	90.6 ± 19.3	.054†
BMI (kg/m^2), mean (SD)	30.7 (6.12)	31.8 (6.10)	.026
eGFR category (mL/min/1.73 m^2), n (%)			.967†
Moderate impairment, ≥30 to <60	23 (7.6)	24 (7.8)	
Mild impairment, ≥60 to <90	180 (59.4)	184 (60.1)	
Normal, ≥90	100 (33.4)	98 (32.0)	
Chronic kidney disease, n (%)	24 (7.9)	24 (7.8)	>.999*
Diabetes, n (%)	31 (10.2)	35 (11.4)	.696*

AZL-M/CLD = azilsartan medoxomil/chlorthalidone single-pill combination; AZL-M + HCTZ = azilsartan medoxomil + hydrochlorothiazide co-administered; BMI = body mass index; eGFR = estimated glomerular filtration rate; SD = standard deviation.

*Two-sided *P* value (exact) based on Pearson chi-square test.

†Two-sided *P* value based on 2-sample *t* test.

‡Two-sided *P* value (exact) based on Pearson chi-square test, with mutually exclusive race categories (ie, multiracial subjects not counted under each race component). The analysis is based on 3 race categories: Caucasian, black or African American, and other. The following races are grouped into the "other" category: American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and Multiple.

chlorothiazide groups, respectively. Consecutive elevations of serum creatinine ≥50% from baseline and greater than the upper limit of normal were similar in the azilsartan medoxomil/chlorthalidone and azilsartan medoxomil + hydrochlorothiazide groups (3 [1.0%] vs 1 [0.3%], respectively). Serum potassium levels <3.4 mmol/L were observed in 5 participants (1.7%) and 1 participant (0.3%) in the azilsartan medoxomil/chlorthalidone and azilsartan medoxomil + hydrochlorothiazide groups, respectively. There were 2 unwitnessed, sudden deaths of unknown cause, 1 in each group.

DISCUSSION

The results of this superiority study indicate that chlorthalidone combined with azilsartan medoxomil results in more effective blood pressure reduction and control rates compared with hydrochlorothiazide combined with azilsartan medoxomil, at comparable doses of diuretic. This superiority of azilsartan medoxomil/chlorthalidone on blood pressure lowering also was evident on ambulatory blood pressures after 4 weeks of combination therapy. The azilsartan medoxomil/chlorthalidone combination is well tolerated with a side effect profile similar to that of azilsartan medoxomil + hydrochlorothiazide. The use of azilsartan medoxomil/chlorthalidone as combination therapy is more likely to achieve blood pressure goals compared with a similar combination with hydrochlorothiazide.

Between group differences in systolic blood pressure of >5 mm Hg favoring the azilsartan medoxomil/chlorthalidone combination were observed in this study. When this blood pressure difference is applied to large cohorts, it would be predicted to translate into more than a 20% cardiovascular event relative risk reduction with the azilsartan medoxomil/chlorthalidone combination over azilsartan medoxomil + hydrochlorothiazide.[13,14]

One of the reasons chlorthalidone fell out of favor many years ago was its proclivity to generate hypokalemia, which may increase mortality among patients with hypertension.[15] This concern was raised in the early 1980s before widespread use of renin-angiotensin-aldosterone system blockers

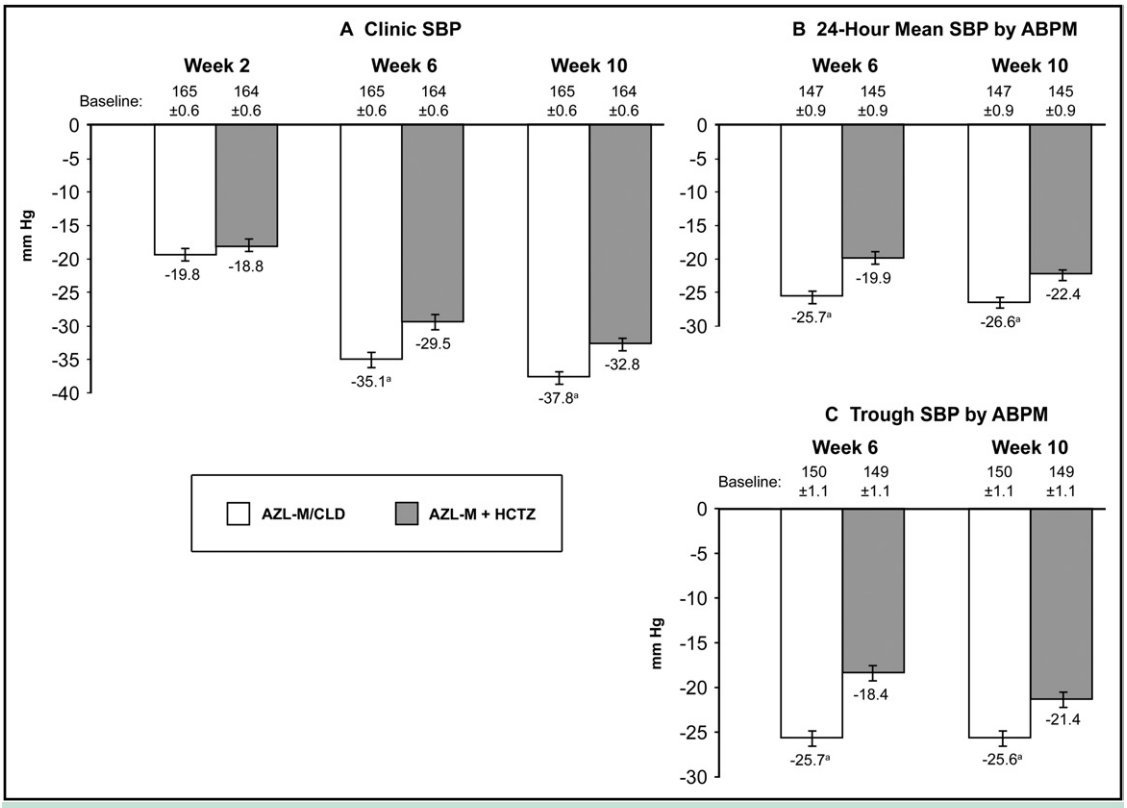

Figure 3 Change from baseline in (**A**) clinic systolic blood pressure and (**B**) 24-hour mean systolic blood pressure and (**C**) trough (22-24 hours after dosing) systolic blood pressure assessed by ambulatory blood pressure monitoring. The diuretic dose was to be up-titrated from 12.5 to 25 mg for participants who had not achieved target blood pressure at week 6 (n [%]): 93 (30.8%) for AZL-M/CLD versus 139 (45.9%) for AZL-M + HCTZ. [a]$P \leq .001$ for comparison of AZL-M/CLD versus AZL-M + HCTZ. Data are least-squares mean ± standard error of the mean. ABPM = ambulatory blood pressure monitoring; AZL-M/CLD = azilsartan medoxomil/chlorthalidone single-pill combination; AZL-M + HCTZ = azilsartan medoxomil + hydrochlorothiazide co-administered; SBP = systolic blood pressure.

and potassium supplements and when chlorthalidone doses averaged between 50 and 100 mg per day. In this and other more recent trials, such high doses were shown to be unnecessary for benefit,[8,9] and thus the incidence of hypokalemia is reduced. In this trial, hypokalemia was uncommon with chlorthalidone or hydrochlorothiazide in combination

Table 2 Change From Baseline in Clinic Diastolic Blood Pressure and 24-Hour Mean Diastolic Blood Pressure

Study Visit	AZL-M/CLD	AZL-M + HCTZ	Difference	*P* Value
Clinic diastolic pressure	N = 295	N = 292		
Baseline	95.5 ± 0.5	95.5 ± 0.6	—	.972
Week 2	−7.1 ± 0.5	−6.0 ± 0.5	−1.0 (−2.5 to 0.4)	.153
Week 6†	−15.0 ± 0.6	−11.2 ± 0.55	−3.7 (−5.2 to −2.2)	<.001
Week 10	−16.4 ± 0.5	−13.7 ± 0.5	−2.7 (−4.1 to −1.3)	<.001
24-h mean diastolic pressure	N = 227	N = 230		
Baseline	85.9 ± 0.7	86.5 ± 0.7	—	—
Week 6*†	−14.7 ± 0.6	−10.9 ± 0.6	−3.8 (−5.5 to −2.1)	<.001
Week 10	−15.2 ± 0.5	−12.6 ± 0.5	−2.6 (−4.1 to −1.1)	<.001

AZL-M/CLD = azilsartan medoxomil/chlorthalidone single-pill combination; AZL-M + HCTZ = azilsartan medoxomil + hydrochlorothiazide co-administered.

Data are the least-squares mean ± standard error or least-squares mean (95% CI), with last observation carried forward.

*AZL-M/CLD n = 179, AZL-M + HCTZ n = 162 at week 6 only.

†Diuretic dose was to be up-titrated from 12.5 to 25 mg for participants who had not achieved target blood pressure at week 6 (n [%]): 93 (30.8%) for AZL-M/CLD versus 139 (45.9%) for AZL-M + HCTZ.

Table 3 Proportion of Participants Achieving Both Systolic and Diastolic Target Blood Pressures by Visit

Study Visit	AZL-M/CLD N = 295	AZL-M + HCTZ N = 292	Odds Ratio	*P* Value
Week 6*	189 (64.1)	134 (45.9)	2.25 ± 0.40 (1.59-3.17)	<.001
Week 10	211 (71.5)	182 (62.3)	1.57 ± 0.29 (1.10-2.24)	.013

AZL-M/CLD = azilsartan medoxomil/chlorthalidone single-pill combination; AZL-M + HCTZ = azilsartan medoxomil + hydrochlorothiazide co-administered.

Data are n (%) or odds ratio ± standard error (95% CI), with last observation carried forward.

*Diuretic dose was to be up-titrated from 12.5 to 25 mg at week 6 if target blood pressure had not been achieved. Participants who discontinued the study before week 6 were included in the analysis by the last observation carried forward method; therefore, the percentage of participants whose diuretic dose was up-titrated at week 6 (**Figure 1**) was lower than would be expected on the basis of the percentage of participants with uncontrolled blood pressure at week 6.

with azilsartan medoxomil and was rarely a cause of treatment discontinuation.

Higher achievement of blood pressure goals, especially in the presence of a renin-angiotensin-aldosterone system blocker, may be associated with an acute increase in serum creatinine. In patients with renal insufficiency, it is common for serum creatinine to increase as much as 30% to 35% after initiation of angiotensin receptor blockers or angiotensin-converting enzyme inhibitors, especially if blood pressure decreases to <140/90 mm Hg when chronically elevated at ≥ 20 to 40 mm Hg above this level.[16] Patients with chronic hypertension and subsequent endothelial dysfunction may be more susceptible to this phenomenon because of less effective autoregulation of renal blood flow.[17] How-

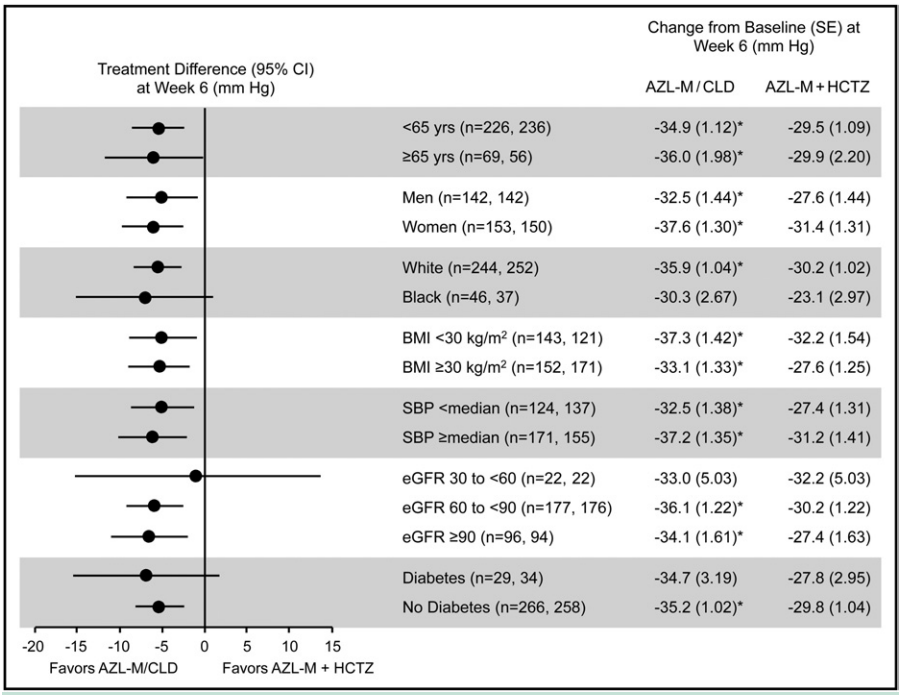

Figure 4 Subgroup analyses for change from baseline to week 6 in clinic SBP by baseline characteristics. Closed circles (●) represent the treatment difference between the AZL-M/CLD group and the AZL-M + HCTZ group. The median clinic SBP at baseline was 162.7 mm Hg. Baseline estimated glomerular filtration rate categories expressed as mL/min/1.73 m^2. *P <.05 versus AZL-M + HCTZ. Data are least-squares mean change from baseline. AZL-M/CLD = azilsartan medoxomil/chlorthalidone single-pill combination; AZL-M + HCTZ = azilsartan medoxomil + hydrochlorothiazide co-administered; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure; SE = standard error.

Table 4 Overview of Adverse Events

Event	AZL-M/CLD N = 302	AZL-M + HCTZ N = 303	*P* Value
Any adverse event	158 (52.3)	144 (47.5)	.255
Most common adverse events (≥2% in either group)			
Dizziness	37 (12.3)	32 (10.6)	.525
Serum creatinine increased*	39 (12.9)	27 (8.9)	.120
Headache	16 (5.3)	16 (5.3)	>.999
Fatigue	11 (3.6)	10 (3.3)	.829
Asthenia	9 (3.0)	6 (2.0)	.448
Hypotension	7 (2.3)	3 (1.0)	.222
Upper respiratory tract infection	4 (1.3)	6 (2.0)	.752
Adverse events resulting in study drug discontinuation†	28 (9.3)	22 (7.3)	.380
Serious adverse events	6 (2.0)	5 (1.7)	
Death‡	1 (0.3)	1 (0.3)	

AZL-M/CLD = azilsartan medoxomil/chlorthalidone single-pill combination; AZL-M + HCTZ = azilsartan medoxomil + hydrochlorothiazide co-administered.

Data are participants n (%).

*Investigators were instructed to report any serum creatinine elevation ≥ 30% from baseline and greater than the upper limit of normal as an adverse event of special interest.

†Proportion of adverse events that resulted in patients needing to discontinue study drug.

‡Two sudden deaths were considered not related (n = 1, AZL-M/CLD group) or possibly related (n = 1, AZL-M + HCTZ group) to the study drug by the investigators.

ever, a systematic review of clinical studies using renin-angiotensin-aldosterone system blockade with a primary renal outcome end point demonstrates that a sustained and early increase of 30% to 35% in serum creatinine is associated with a slower decline in kidney function over the next 6 to 7 years.[18] Not only renin-angiotensin-aldosterone system blockade but also the magnitude of blood pressure reduction was associated with early increases of serum creatinine.[18] This magnitude of increase in serum creatinine has been observed in renal outcome trials in which renin-angiotensin-aldosterone system blockers demonstrated a marked slowing of diabetic kidney disease progression.[19,20] Thus, small sustained increases in creatinine elevations may not reflect a true adverse effect, but rather a physiologic response to effective volume and blood pressure reduction. In this study, investigator reports of increased serum creatinine of this magnitude were slightly more common with the single-pill combination azilsartan medoxomil/chlorthalidone than with co-administration of azilsartan medoxomil with hydrochlorothiazide, albeit not significantly (**Table 4**). However, these reports of increased creatinine were based on single elevations and are contrasted by the relatively low frequency of consecutive elevations, indicating that creatinine increases were reversible and consistent with hemodynamic rather than structural changes in the kidney. Although this study was not powered to assess the impact of changes in serum creatinine, other long-term studies using chlorthalidone do not demonstrate adverse renal effects.[21,22]

Study Limitations

A study limitation is the relatively low proportion of elderly (22%) and black (14%) participants. Because previous studies with azilsartan medoxomil clearly demonstrated antihypertensive efficacy in black participants,[12] and subgroup analyses of chlorthalidone outcome trials have shown cardiovascular event risk reduction in black participants with hypertension,[23] additional studies in this population will be important.

CONCLUSIONS

Chlorthalidone in combination with azilsartan medoxomil decreased blood pressure more effectively than hydrochlorothiazide in combination with azilsartan medoxomil at equal or higher hydrochlorothiazide doses. Furthermore, because azilsartan medoxomil has greater efficacy compared with other angiotensin receptor blockers (eg, valsartan and olmesartan) on 24-hour ambulatory monitoring,[10-12] the combination of this angiotensin receptor blocker with chlorthalidone may be an effective therapeutic option to achieve blood pressure control in patients at high cardiovascular risk.

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