

## Azilsartan Medoxomil Plus Chlorthalidone Reduces Blood Pressure More Effectively Than Olmesartan Plus Hydrochlorothiazide in Stage 2 Systolic Hypertension

William C. Cushman, George L. Bakris, William B. White, Michael A. Weber, Domenic Sica, Andrew Roberts, Eric Lloyd, Stuart Kupfer

**Abstract**—Azilsartan medoxomil, an effective, long-acting angiotensin II receptor blocker, is a new treatment for hypertension that is also being developed in fixed-dose combinations with chlorthalidone, a potent, long-acting thiazide-like diuretic. We compared once-daily fixed-dose combinations of azilsartan medoxomil/chlorthalidone force titrated to a high dose of either 40/25 mg or 80/25 mg with a fixed-dose combination of the angiotensin II receptor blocker olmesartan medoxomil plus the thiazide diuretic hydrochlorothiazide force titrated to 40/25 mg. The design was a randomized, 3-arm, double-blind, 12-week study of 1071 participants with baseline clinic systolic blood pressure 160 to 190 mm Hg and diastolic blood pressure  $\leq$ 119 mm Hg. Patients had a mean age of 57 years; 59% were men, 73% were white, and 22% were black. At baseline, mean clinic blood pressure was 165/96 mm Hg and 24-hour mean blood pressure was 150/88 mm Hg. Changes in clinic (primary end point) and ambulatory systolic blood pressures at week 12 were significantly greater in both azilsartan medoxomil/chlorthalidone arms than in the olmesartan/hydrochlorothiazide arm ( $P < 0.001$ ). Changes in clinic systolic blood pressure (mean  $\pm$  SE) were  $-42.5 \pm 0.8$ ,  $-44.0 \pm 0.8$ , and  $-37.1 \pm 0.8$  mm Hg, respectively. Changes in 24-hour ambulatory systolic blood pressure were  $-33.9 \pm 0.8$ ,  $-36.3 \pm 0.8$ , and  $-27.5 \pm 0.8$  mm Hg, respectively. Adverse events leading to permanent drug discontinuation occurred in 7.9%, 14.5%, and 7.1% of the groups given azilsartan medoxomil/chlorthalidone 40/25 mg, azilsartan medoxomil/chlorthalidone 80/25 mg, and olmesartan/hydrochlorothiazide 40/25 mg, respectively. This large, forced-titration study has demonstrated superior antihypertensive efficacy of azilsartan medoxomil/chlorthalidone fixed-dose combinations compared with the maximum approved dose of olmesartan/hydrochlorothiazide. (*Hypertension*. 2012;60:310-318.) • **Online Data Supplement**

**Key Words:** hypertension ■ azilsartan medoxomil ■ angiotensin receptor blocker ■ chlorthalidone ■ thiazide-like diuretic ■ antihypertensive therapy

Although control of hypertension in the United States has improved substantially over the past decade, 31% of people who are treated for hypertension are not controlled to a blood pressure (BP) level  $< 140/90$  mm Hg.<sup>1</sup> Therefore, there is a need for more effective antihypertensive regimens that include simple single-pill fixed-dose combination (FDC) products.

Azilsartan medoxomil is a newly approved, effective, long-acting angiotensin II receptor blocker (ARB). It is a prodrug that is quickly hydrolyzed to the active moiety azilsartan, a potent and selective ARB with estimated bioavailability of 60% and elimination half-life of 12 hours.<sup>2</sup> At its maximal dose, azilsartan medoxomil has superior efficacy

compared with both olmesartan and valsartan at their maximum, approved doses, without increasing adverse events.<sup>3-5</sup> Chlorthalidone is a potent, long-acting thiazide-like diuretic that has a strong evidence base supporting cardiovascular benefit from randomized, controlled clinical trials.<sup>6-12</sup> It is also more effective in lowering BP than the more commonly used thiazide diuretic, hydrochlorothiazide.<sup>13</sup> Therefore, combinations of azilsartan medoxomil and chlorthalidone are being developed as an effective 2-drug FDC.

The present multicenter study is a large, forced-titration, active-comparator study of an ARB-chlorthalidone combination. We compared the antihypertensive efficacy, safety, and tolerability of azilsartan medoxomil plus chlorthalidone with

Received November 22, 2011; first decision December 15, 2011; revision accepted May 16, 2012.

From the University of Tennessee College of Medicine (W.C.C.), Memphis, TN; The University of Chicago Medicine (G.L.B.), Chicago, IL; University of Connecticut School of Medicine (W.B.W.), Farmington, CT; Downstate Medical Center (M.A.W.), Brooklyn, NY; Virginia Commonwealth University (D.S.), Richmond, VA; Takeda Global Research and Development Center, Inc (A.R., E.L., S.K.), Deerfield, IL.

There was no payment by the sponsor to any non-Takeda authors for their work in analyzing data, writing, or editing of this article.

This trial has been registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (identifier NCT01033071).

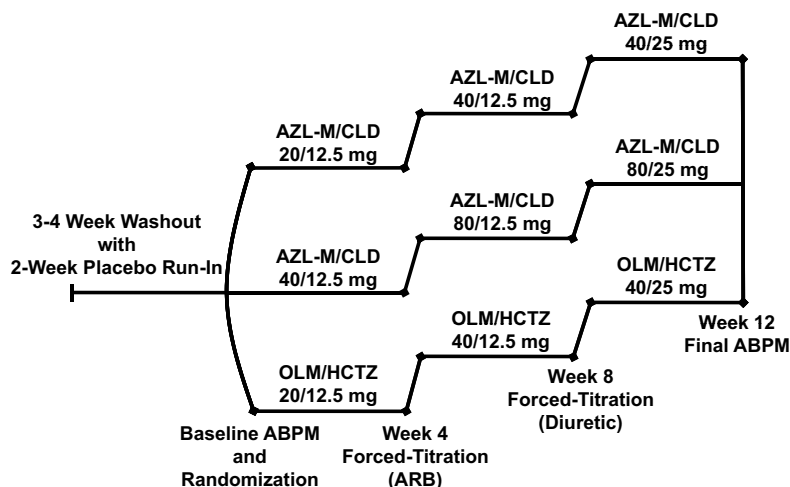
The online-only Data Supplement is available with this article at <http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.111.188284/-DC1>.

Correspondence to William C. Cushman, 127 Harbor Town Blvd, Memphis, TN 38103. E-mail [wcushman@pol.net](mailto:wcushman@pol.net)

© 2012 American Heart Association, Inc.

*Hypertension* is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.111.188284



**Figure 1.** Treatments and titration schedule. AZL-M/CLD indicates azilsartan medoxomil/chlorthalidone; OLM/HCTZ, olmesartan/hydrochlorothiazide; ABPM, ambulatory blood pressure monitoring.

the ARB olmesartan medoxomil plus hydrochlorothiazide in participants with stage 2 systolic hypertension. Measurement of both clinic and ambulatory BPs was used to assess antihypertensive efficacy.

## Methods

### Study Design

This was a randomized, double-blind, forced-titration study comparing the antihypertensive efficacy and safety of an FDC containing azilsartan medoxomil and chlorthalidone with an FDC containing olmesartan medoxomil and hydrochlorothiazide in patients with stage 2 primary systolic hypertension. Before randomization, all of the patients received 2 weeks of single-blind treatment with placebo only. Previously treated patients stopped taking their antihypertensive medications 1 to 2 weeks before the placebo run-in, resulting in a 3- to 4-week washout of all BP-lowering agents. After the washout/run-in was complete, eligible patients were randomized to 12 weeks of double-blind treatment with one of the following dosing strategies: (1) azilsartan medoxomil/chlorthalidone 20/12.5 mg → 40/12.5 mg → 40/25.0 mg; (2) azilsartan medoxomil/chlorthalidone 40/12.5 mg → 80/12.5 mg → 80/25.0 mg; or (3) olmesartan/hydrochlorothiazide 20/12.5 mg → 40/12.5 mg → 40/25.0 mg. In each group, drug was force titrated regardless of BP at weeks 4 and 8 (Figure 1). Treatment assignment was stratified by race (ie, black or nonblack).

### Patients

Men and women who were ≥18 years of age and had primary hypertension were recruited from 130 investigative sites in the United States and Canada. The protocol conformed to the Declaration of Helsinki and regional regulatory guidelines, and the study was reviewed and approved by regional institutional review boards. Before initiating any study procedures, each patient was informed of the study details and signed an institutional review board–approved informed consent form. At randomization, each patient was required to have a clinic, seated systolic BP (SBP) ≥160 and ≤190 mm Hg. Exclusion criteria included known or suspected secondary hypertension or severe diastolic hypertension (>119 mm Hg); severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1.73 m<sup>2</sup>); known or suspected renal artery stenosis; clinically relevant or unstable cardiovascular diseases within 6 months of enrollment; poorly controlled diabetes mellitus (hemoglobin A1c >8.0%); clinically significant hepatic abnormalities; or abnormal potassium levels (ie, above or below the reference range). A baseline ambulatory BP monitoring (ABPM) reading of insufficient quality, poor compliance during the placebo run-in period, and nightshift work were also exclusions. In addition, pregnant or nursing women and women of childbearing potential not using medically approved

means of contraception were excluded. Concomitant use of other antihypertensive agents or medications known to affect BP was not allowed. Potassium supplementation was not excluded and could be adjusted or initiated at the investigator's discretion.

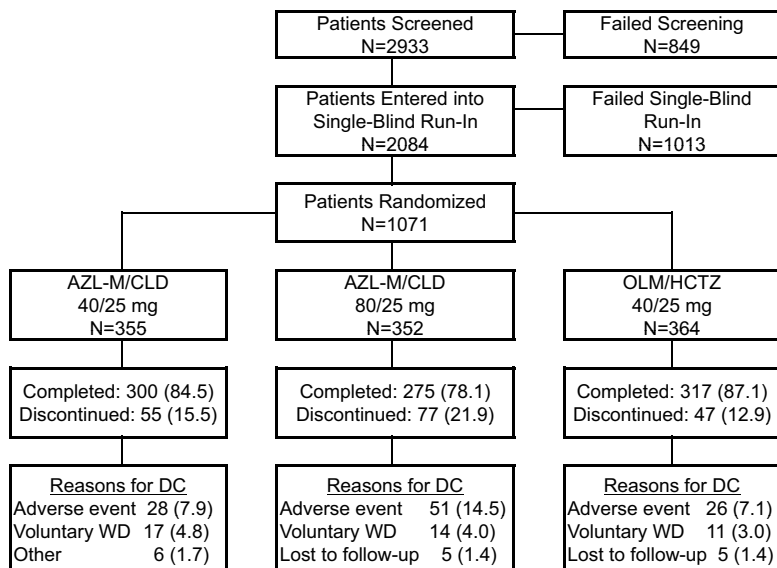
### BP and Assessments

Clinic BP was measured at baseline and each postrandomization visit (weeks 2, 4, 8, 10, and 12) using a manual, mercury-free device with an indicator display to assist in applying a 2-mm Hg/s deflation rate (Greenlight 300 sphygmomanometer; Accoson, Harlow, United Kingdom).<sup>14</sup> Three clinic BP measurements were obtained at 2-minute intervals ≈24 hours after the previous dose of study medication and after the patient was seated with back supported for 5 minutes without talking. In addition, a single BP measurement was obtained after the patient remained standing for 2 minutes to evaluate for orthostatic hypotension.

Ambulatory BP was recorded with a portable, automated device (model 90207, SpaceLabs, Inc, Issaquah, WA)<sup>15</sup> during the 24 hours before randomization and during the 24 hours after the final dose of double-blind treatment at the week 12 visit; for subjects who discontinued prematurely, a final ABPM was attempted if the subject received ≥4 weeks of double-blind treatment. Ambulatory BP was measured every 15 minutes between 6:00 AM and 10:00 PM and every 20 minutes between 10:00 PM and 6:00 AM. Minimum quality control criteria for the ABPM readings included a starting time of 8:00 AM ±2 hours, a monitoring period of ≥24 hours, record of ≥80% of the expected BP readings, ≤2 nonconsecutive hours with <1 valid BP reading, and no consecutive hours with <1 valid BP reading. If a recording was unsuccessful, the treatment period could be extended and the ABPM could be repeated within 4 to 5 days. If the repeat recording failed, the ambulatory BP data were considered nonevaluable.

### Safety Assessments

Safety monitoring procedures included recording of adverse events, clinical laboratory test results, vital sign measurements, ECG findings, 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 ≥30% from baseline and more than the upper limit of normal as an adverse event of special interest. Patients with creatinine values ≥50% from baseline and more than the upper limit of normal were to be considered for discontinuation if confirmed by a repeat test within 5 to 7 days. Safety laboratory parameters were evaluated at each visit, with key laboratory parameters including those related to renal function (serum creatinine and serum urea nitrogen), electrolyte homeostasis (serum potassium, sodium, chloride, calcium, and



**Figure 2.** Patient disposition. Data are n (%). DC indicates discontinuation; WD, withdrawal; AZL-M/CLD, azilsartan medoxomil/chlorthalidone; OLM/HCTZ, olmesartan/hydrochlorothiazide. The 3 most common reasons for permanent discontinuation from the study are listed.

magnesium), and metabolic function (serum uric acid, glucose, and fasting lipids).

## Statistical Analyses

### End Points

The primary end point was change from baseline in trough ( $\approx$ 24 hours postdose), seated, clinic SBP at week 12. Secondary end points included changes from baseline in clinic diastolic BP (DBP), 24-hour mean SBP and DBP measured by ABPM, and other ABPM parameters, including trough mean BP (22–24 hours postdosing). The proportion of subjects who achieved various BP targets was also calculated.

### Analysis of End Points

The primary end point was evaluated using an ANCOVA with treatment as fixed effect and the baseline clinic SBP as the covariate. All of the statistical tests were 2 sided at the 5% significance level, and results were presented with 95% CIs and *P* values. Type 1 error was controlled using the principle of “closed” testing, in which the hypothesis that “all treatment groups are equal” was tested first; on rejection of this hypothesis, the 2 pairwise comparisons (ie, each azilsartan medoxomil/chlorthalidone group versus the olmesartan/hydrochlorothiazide group) were performed. Secondary clinic and ambulatory BP end points were analyzed with a similar statistical model. Analyses of the clinic BP measurements were based on the last observation carried forward method. A logistic model with treatment as fixed effect and baseline value as a covariate was used in the analyses of target BP achievement; an odds ratio and associated 95% CI were estimated. Subgroup analyses were performed for each end point by age (<65 years or  $\geq$ 65 years), sex, race (black, white, or other), baseline clinic SBP (less than median or at or more than median), body mass index (<30 or  $\geq$ 30 kg/m<sup>2</sup>), renal function (estimated glomerular filtration rate  $\geq$ 90 [normal],  $\geq$ 60 to <90 [mild impairment], or  $\geq$ 30 to <60 mL/min per 1.73 m<sup>2</sup> [moderate impairment]), and diabetes mellitus. For the above subgroups, post hoc analyses were performed on the primary end point and analysis by including the subgroup as a fixed effect to the ANCOVA along with the treatment subgroup interaction.

### Sample Size

A sample size of 1050 randomized subjects (350 per group) was determined as sufficient to achieve  $\geq$ 90% power to detect a difference of 3.75 mm Hg between the azilsartan medoxomil/chlorthalidone groups and the olmesartan/hydrochlorothiazide group for the primary end point of clinic SBP, assuming a 2-sided

significance level of 5%, an SD of 14 mm Hg, and a 15% dropout rate.

## Results

### Patient Disposition and Demographics

Of the 2933 patients screened, 2084 (71%) were enrolled in the placebo run-in period, and of these 1071 (51%) met the entry criteria and were randomized. Participants were randomized to 1 of 3 active treatment groups (352–364 per group); 892 (83%) randomized patients completed the study as planned (Figure 2). The percentage of patients who completed the study was similar for the azilsartan medoxomil/chlorthalidone 40/25 mg (85%) and olmesartan/hydrochlorothiazide (87%) groups but lower for the azilsartan medoxomil/chlorthalidone 80/25 mg group (78%). The most common reasons for discontinuation were adverse events and voluntary withdrawal (Figure 2).

Demographic characteristics were similar between treatment groups (Table 1). In the overall study population, mean age was 57 years, and 59% of subjects were men, 73% were white, and 22% were black. Across treatment groups, mean trough clinic BP was 165/96 mm Hg. The majority of patients had mild (64%) or moderate (8%) renal impairment. Seventeen percent of patients had diabetes mellitus per medical history. Baseline use of potassium supplementation was similar across treatment groups, ranging from 0.8% to 1.6%. Initiation of potassium supplementation during the study was uncommon, at 1.9% in the olmesartan/hydrochlorothiazide group and 0.3% to 0.5% in the azilsartan-medoxomil/chlorthalidone groups.

### Changes in SBP

Reductions in clinic SBP at week 12 (the primary end point) in both azilsartan medoxomil/chlorthalidone groups were statistically significantly greater than reductions achieved with olmesartan/hydrochlorothiazide (Table 2); the treatment difference and corresponding 95% CI between the azilsartan medoxomil/chlorthalidone and olmesartan/hydrochlorothiazide groups were  $-5.3$  mm Hg ( $-7.6$  to  $-3.1$  mm Hg;

**Table 1. Demographic and Baseline Characteristics**

Characteristic	AZL-M/CLD 40/25 mg (N=355)	AZL-M/CLD 80/25 mg (N=352)	OLM/HCTZ 40/25 mg (N=364)
Sex, n (%)			
Male	223 (62.8)	201 (57.1)	205 (56.3)
Female	132 (37.2)	151 (42.9)	159 (43.7)
Age, y, mean (SD)	56.4 (10.5)	56.7 (10.1)	56.7 (10.9)
Race, n (%)*			
American Indian or Alaska Native	2 (0.6)	5 (1.4)	5 (1.4)
Asian	13 (3.7)	11 (3.1)	11 (3.0)
Black	80 (22.5)	80 (22.7)	80 (22.0)
White	261 (73.5)	258 (73.3)	267 (73.4)
Prior use of antihypertensive therapy, n (%)	273 (76.9)	281 (79.8)	277 (76.1)
Diabetes mellitus, n (%)	54 (15.2)	59 (16.8)	65 (17.9)
eGFR, n (%)†			
≥30 to <60 mL/min per 1.73 m <sup>2</sup>	26 (7.3)	29 (8.2)	25 (6.9)
≥60 to <90 mL/min per 1.73 m <sup>2</sup>	224 (63.1)	220 (62.5)	246 (67.6)
≥90 mL/min per 1.73 m <sup>2</sup>	105 (29.6)	103 (29.3)	91 (25.0)
BMI, kg/m <sup>2</sup> , mean (SD)	31.4 (5.94)	31.9 (6.59)	31.6 (5.92)
Blood pressure, mm Hg, mean (SD)			
Clinic SBP/DBP	164.9 (10.1)/96.1 (9.8)	164.8 (10.4)/95.9 (9.8)	164.7 (9.9)/95.2 (10.3)
Trough BP‡ SBP/DBP	153.0 (16.8)/92.5 (12.5)	154.5 (16.8)/92.4 (12.1)	152.8 (16.5)/91.5 (12.2)
24-h mean SBP/DBP	149.3 (13.6)/88.1 (10.9)	150.8 (13.8)/88.4 (10.9)	149.2 (14.0)/87.1 (11.0)

AZL-M/CLD indicates azilsartan medoxomil/chlorthalidone; OLM/HCTZ, olmesartan/hydrochlorothiazide. SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate.

\*Patients may have chosen >1 category for race.

†One patient had an eGFR <30 mL/min per 1.73 m<sup>2</sup>, and 1 had a missing baseline value (both in the OLM/HCTZ group).

‡Data were measured during the last 2 hours of the ambulatory BP recording.

$P < 0.001$ ) in favor of the azilsartan medoxomil/chlorthalidone 40/25 mg group and  $-6.9$  mm Hg ( $-9.2$  to  $-4.6$ ;  $P < 0.001$ ) in favor of the azilsartan medoxomil/chlorthalidone 80/25 mg group. Statistically significant reductions in favor of both azilsartan medoxomil/chlorthalidone groups were also seen for clinic SBP at all of the other study visits (ie, weeks 2, 4, 8, and 10).

Ambulatory BP results were consistent with the clinic data; there were statistically significantly greater SBP reductions in both of the azilsartan medoxomil/chlorthalidone groups compared with olmesartan/hydrochlorothiazide at week 12 at each hour of the 24-hour ABPM intervals (Figure 3). Accordingly, reductions in 24-hour mean and trough SBP by ABPM at week 12 were also statistically significantly greater for both azilsartan medoxomil/chlorthalidone groups compared with the olmesartan/hydrochlorothiazide group ( $P < 0.001$  for each comparison; Table 2).

### Changes in DBP

As with the SBP results, there were significantly greater reductions in clinic DBP in both azilsartan medoxomil/chlorthalidone groups compared with olmesartan/hydrochlorothiazide at week 12 (Table 2). Significantly greater DBP reductions were also maintained at each study visit (ie, weeks 2, 4, 8, and 10) for the clinic measurements and at each hour of the 24-hour ABPM recording at week 12 (data not shown).

### Target Clinic BP Achievement

The percentage of patients who achieved an SBP of <140 mm Hg was statistically significantly greater with azilsartan medoxomil/chlorthalidone 80/25 mg (87.3%) compared with olmesartan/hydrochlorothiazide 40/25 mg (80.2%;  $P = 0.007$ ) but not significantly different for azilsartan medoxomil/chlorthalidone 40/25 mg (84.9%) versus olmesartan/hydrochlorothiazide ( $P = 0.08$ ). Both azilsartan medoxomil/chlorthalidone groups had statistically significantly more subjects reach an SBP of <130 or <120 mm Hg compared with the olmesartan/hydrochlorothiazide group. Similarly, the percentage of patients who achieved a target BP of <140/90 mm Hg (81.4%, 83.9%, and 74.6%) or <130/80 mm Hg (56.1%, 60.6%, and 41.0%) was significantly greater in both azilsartan medoxomil/chlorthalidone groups than the olmesartan/hydrochlorothiazide group (see Figure S1 in the online-only Data Supplement).

### Changes in Clinic SBP by Baseline Subgroups

Significantly greater BP reductions were observed in patients who received azilsartan medoxomil/chlorthalidone relative to olmesartan/hydrochlorothiazide in nearly all of the subgroups (see Figure S2 in the online-only Data Supplement). There was no statistical evidence that the treatment differences were dependent on age, sex, race, baseline hypertension severity, body mass index, renal function, or diabetes mellitus ( $P > 0.10$ ).

**Table 2. Change From Baseline in Clinic Blood Pressure and Trough and 24-h Mean Blood Pressure by ABPM**

Parameter	AZL-M/CLD 40/25 mg	AZL-M/CLD 80/25 mg	OLM/HCTZ 40/25 mg	AZL-M/CLD 40/25 mg	AZL-M/CLD 80/25 mg	OLM-M/HCTZ 40/25 mg
	Clinic SBP			Clinic DBP		
N	344	330	354	344	330	354
Baseline	164.8±0.5	165.0±0.6	164.6±0.5	96.1±0.5	95.9±0.6	95.3±0.5
Change at wk 4	-34.7±0.8*	-36.7±0.8*	-29.7±0.8	-14.9±0.5*	-15.8±0.5*	-11.7±0.5
Change at wk 8	-39.1±0.8*	-39.4±0.8*	-33.5±0.8	-17.0±0.5*	-17.7±0.5*	-13.9±0.5
Change at wk 12	-42.5±0.8*	-44.0±0.8*	-37.1±0.8	-18.8±0.5*	-20.5±0.5*	-16.4±0.5
Difference†	-5.3 (-7.6 to -3.1)	-6.9 (-9.2 to -4.6)	...	-2.3 (-3.6 to -1.0)	-4.1 (-5.4 to -2.8)	...
	Trough SBP by ABPM (h 22–24)			Trough DBP by ABPM (h 22–24)		
N	232	214	238	232	214	238
Baseline	154.4±1.0	156.6±1.1	154.3±1.0	93.1±0.8	93.3±0.8	92.2±0.8
Change at wk 12	-32.9±0.9*	-34.9±0.9*	-25.9±0.9	-19.8±0.6*	-20.2±0.6*	-16.0±0.5
Difference†	-7.0 (-9.4 to -4.7)	-9.0 (-11.5 to -6.6)	...	-3.9 (-5.4 to -2.4)	-4.3 (-5.8 to -2.7)	...
	24-h Mean SBP by ABPM			24-h Mean DBP by ABPM		
N	232	214	238	232	214	238
Baseline	150.4±0.9	152.2±0.9	150.3±0.8	88.3±0.7	88.9±0.7	87.4±0.7
Change at wk 12	-33.9±0.8*	-36.3±0.8*	-27.5±0.8	-19.4±0.5*	-20.7±0.5*	-16.2±0.4
Difference†	-6.4 (-8.5 to -4.3)	-8.8 (-11.0 to -6.7)	...	-3.2 (-4.5 to -2.0)	-4.5 (-5.8 to -3.3)	...

Blood pressure data are in millimeters of mercury; baseline values and change from baseline values are least squares (LS) mean±SE. Sample sizes reflect the No. of subjects who had both a baseline and final value. AZL-M/CLD indicates azilsartan medoxomil/chlorthalidone; OLM/HCTZ, olmesartan/hydrochlorothiazide; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABPM, ambulatory blood pressure monitoring.

\*Data show statistically significantly greater reduction than olmesartan/hydrochlorothiazide ( $P<0.001$ ).

†Data show LS mean (95% CI) differences in change from baseline vs OLM/HCTZ at wk 12.

### Safety and Tolerability

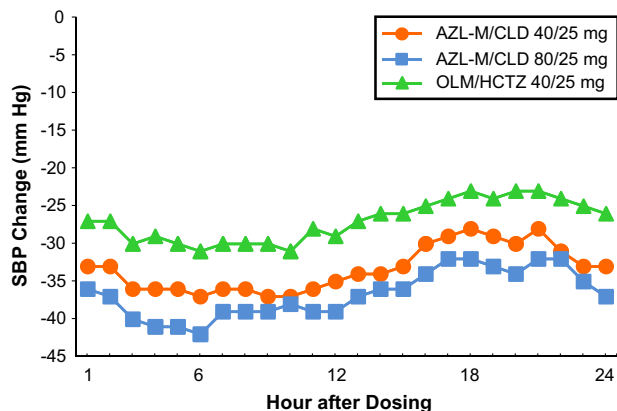
The frequency of total adverse events was higher in the azilsartan medoxomil/chlorthalidone groups compared with olmesartan/hydrochlorothiazide. The most common adverse events included increases in serum creatinine and dizziness, and both of these events occurred more frequently and in a

dose-dependent manner with azilsartan medoxomil/chlorthalidone (Table 3).

Reports of serious events and events that led to discontinuation were similar for azilsartan medoxomil 40/25 mg and olmesartan/hydrochlorothiazide (Figure 2 and Table 3). There was a higher incidence of permanent discontinuation because of adverse events, but not serious adverse events, in the azilsartan medoxomil/chlorthalidone 80/25 mg group, primarily because of dizziness, serum creatinine increases, or hypotension (Table 3).

Consecutive elevations of serum creatinine  $\geq 50\%$  from baseline and more than the upper limit of normal were lower in the azilsartan medoxomil/chlorthalidone 40/25 mg group (1.4%) and higher in the azilsartan medoxomil/chlorthalidone 80/25 mg group (4.4%) compared with the olmesartan/hydrochlorothiazide 40/25 mg group (2.8%; Table 3). For individual patients in all of the treatment groups, creatinine elevations were nonprogressive and associated with relatively large BP and weight reductions. For patients with elevations of serum creatinine  $\geq 50\%$  from baseline and more than the upper limit of normal at the final visit, mean SBP and mean weight decreased 48.9 mm Hg and 3.7 kg from baseline compared with those patients without creatinine elevations (41.6 mm Hg and 0.5 kg). In addition, serum creatinine increases that led to withdrawal were based on laboratory findings only, not associated with clinical complications, and reversed after study drug discontinuation.

Changes in other selected serum laboratory parameters were comparable across groups with the exception of greater



**Figure 3.** Change from baseline in systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM) at each hour at week 12. Data are mean changes from baseline. AZL-M indicates azilsartan medoxomil/chlorthalidone; OLM/HCTZ, olmesartan/hydrochlorothiazide. Both AZL-M/CLD groups led to statistically significantly greater SBP reduction than OLM/HCTZ at each hour after dosing ( $P<0.001$ ). Orange circle, AZL-M/CLD 40/25 mg; blue square, AZL-M/CLD 80/25 mg; green triangle, OLM/HCTZ 40/25 mg.

**Table 3. Summary of Safety Findings**

Parameter	AZL-M/CLD 40/25 mg	AZL-M/CLD 80/25 mg	OLM/HCTZ 40/25 mg
N	355	352	364
Any AE	253 (71.3)	249 (70.7)	219 (60.2)
Most common AEs			
Blood creatinine increased	66 (18.6)	78 (22.2)	34 (9.3)
Dizziness	41 (11.5)	58 (16.5)	29 (8.0)
Fatigue	33 (9.3)	14 (4.0)	16 (4.4)
Headache	19 (5.4)	13 (3.7)	26 (7.1)
Blood uric acid increased	19 (5.4)	17 (4.8)	12 (3.3)
Serious AEs	1 (0.3)	10 (2.8)	8 (2.2)
AEs leading to discontinuation*			
Dizziness	4 (1.1)	13 (3.7)	4 (1.1)
Blood creatinine increased	3 (0.8)	12 (3.4)	4 (1.1)
Hypotension	1 (0.3)	12 (3.4)	1 (0.3)
Serum laboratory parameters of interest†			
Creatinine: $\geq 2$ consecutive elevations ( $\geq 1.5 \times$ baseline and $>ULN$ )	5/349 (1.4)	15/340 (4.4)	10/360 (2.8)
Fasting glucose:			
Shifts from $<126$ mg/dL to $\geq 126$ mg/dL	27/313 (8.6)	30/307 (9.8)	26/319 (8.2)
Shifts from $\geq 126$ mg/dL to $<126$ mg/dL	18/42 (42.9)	12/45 (26.7)	15/45 (33.3)
Potassium: shifts from normal to below normal ( $<3.4$ mmol/L)	11/348 (3.2)	5/332 (1.5)	5/352 (1.4)
Low sodium ( $<130$ mmol/L)	10/349 (2.9)	18/339 (5.3)	8/360 (2.2)
High uric acid (M $>10.5$ mg/dL; F $>8.5$ mg/dL)	54/346 (15.6)	65/336 (19.3)	26/359 (7.2)

Data are n (%). AZL-M indicates azilsartan-medoxomil/chlorthalidone; OLM/HCTZ, olmesartan/hydrochlorothiazide; AE, adverse event; M, male; F, female; ULN, upper limit of normal.

\*Data include temporary interruption of study drug or permanent discontinuation from the study; the most common adverse events leading to discontinuation are shown.

†Only laboratory changes judged to be clinically significant by the investigator were reported as AEs.

uric acid increases in the azilsartan medoxomil/chlorthalidone groups; however, reports of gout were infrequent (0.3%, 1.1%, and 0.8% in the azilsartan medoxomil/chlorthalidone 40/25 and 80/25 mg groups and the olmesartan/hydrochlorothiazide 40/25 mg group, respectively). There were more low-sodium values observed with azilsartan medoxomil/chlorthalidone 80/25 mg compared with the other 2 groups (Table 3). There was no notable difference between groups with regard to shifts from normal to elevated fasting glucose levels (Table 3).

## Discussion

This is the first report of a forced-titration comparator study of an ARB-chlorthalidone combination. The forced-titration design provides the most accurate comparison of the antihypertensive efficacy between the drug doses and regimens in a study population with stage 2 hypertension. This study demonstrated superior efficacy of the azilsartan medoxomil/chlorthalidone FDCs compared with the highest approved dose of the olmesartan/hydrochlorothiazide FDC for both clinic and ABPM measurements. At 12 weeks, azilsartan medoxomil/chlorthalidone reduced clinic SBP 5 to 7 mm Hg more and ABPM SBP 7 to 9 mm Hg more than olmesartan/hydrochlorothiazide. The differences in clinic SBP were similar throughout the trial. In addition, 12-week SBP

assessed by 24-hour ABPM was reduced more with azilsartan medoxomil/chlorthalidone than olmesartan/hydrochlorothiazide throughout the 24-hour dosing period. The SBP reductions and control rates for azilsartan medoxomil/chlorthalidone are comparable to what has been reported for triple combinations of olmesartan, amlodipine, and hydrochlorothiazide or similar triple combinations.<sup>16,17</sup> Reductions of clinic SBP were consistently greater in both azilsartan medoxomil/chlorthalidone groups compared with olmesartan/hydrochlorothiazide across multiple subgroups, including blacks.

Tolerability, reflected by discontinuation rates for adverse events, was relatively similar for the lower dose (40/25 mg) of azilsartan medoxomil/chlorthalidone and olmesartan/hydrochlorothiazide, with a moderately higher adverse-event discontinuation rate for the higher dose (80/25 mg) of azilsartan medoxomil/chlorthalidone. Although some of the discontinuations in the 80/25-mg group were attributed to dizziness and hypotension, others were related to protocol-specified discontinuation for consecutive increases of serum creatinine. These creatinine elevations may not reflect a true adverse effect but rather a physiological response to effective volume and BP reduction. In patients with renal insufficiency, it is common for serum creatinine to rise as much as 30% to 35% after initiation of ARBs, especially if BP falls below 140/90 mm Hg when chronically elevated at 20 to 40

mm Hg or more above this level.<sup>18</sup> The mechanism for this fall is in part related to a reduction in intraglomerular pressure secondary to dilation of the efferent arteriole in each glomerulus and reduced systemic pressure transmission at the afferent arteriole.<sup>18,19</sup> Patients with chronic hypertension and subsequent endothelial dysfunction may be more susceptible to this phenomenon because of less effective autoregulation of renal blood flow.<sup>20</sup> In this study, the profile of creatinine elevations was consistent with the expected hemodynamic effects of renin-angiotensin-aldosterone system blockade and intravascular volume contraction, which corresponds with the greater BP and weight reductions observed in patients with creatinine elevations, suggesting that some subjects experienced excessive diuresis. In addition, subjects with creatinine elevations tended to have lower baseline estimated glomerular filtration rate, suggesting less effective autoregulation of renal blood flow in some subjects (data not shown). Finally, the observed reversibility of creatinine elevations further supports functional rather than structural changes in the kidney.

In contrast to historical data showing a high incidence of hypokalemia at chlorthalidone doses of 50 to 100 mg,<sup>21</sup> low serum potassium was relatively infrequent with the azilsartan medoxomil/chlorthalidone combination. This observation is likely related to the lower doses of chlorthalidone (12.5–25.0 mg) used in the combination and the attenuating effect of renin-angiotensin-aldosterone system inhibition associated with azilsartan medoxomil.

Although a number of trials have assessed the antihypertensive efficacy of an ARB-hydrochlorothiazide combination, few have done so in patients with stage 2 hypertension. In a titration-to-target study of valsartan/hydrochlorothiazide,<sup>22</sup> maximum dose 320/25 mg, in men and women  $\geq 70$  years of age with systolic hypertension (mean sitting SBP, 150–200 mm Hg), mean baseline office SBP was 164.4 mm Hg, very similar to the 164.7 to 164.9-mm Hg baseline SBP in the current trial. However, SBP was reduced by only 17.3 mm Hg, which was less than the reductions that we observed. In another study of irbesartan/hydrochlorothiazide in systolic hypertension,<sup>23</sup> SBP was reduced 21.5 mm Hg, although the entry SBP and mean baseline SBP (154.0 mm Hg) were lower than the current study. One open-label study of olmesartan/hydrochlorothiazide in stage 2 systolic hypertension (SBP  $\geq 160.0$  mm Hg) showed a 34.5-mm Hg reduction in SBP with the 40/25-mg dose, comparable to the 37.1-mm Hg SBP reduction in the olmesartan/hydrochlorothiazide arm of the current study with the same doses.<sup>24</sup>

Although a randomized direct comparison of chlorthalidone and hydrochlorothiazide for cardiovascular outcomes is not available, the totality of evidence suggests that chlorthalidone reduces cardiovascular risk more effectively than hydrochlorothiazide at equivalent doses. In a retrospective observational cohort study from the Multiple Risk Factor Intervention Trial, patients treated with chlorthalidone had a 21% lower risk of cardiovascular events than patients treated with hydrochlorothiazide.<sup>6</sup> Chlorthalidone 12.5 to 25 mg/d has demonstrated reduced major cardiovascular outcomes compared with placebo and comparable outcomes compared with a calcium channel blocker and angiotensin-converting

enzyme inhibitor.<sup>10,11</sup> Although 25 to 50 mg/d of hydrochlorothiazide has also been shown to reduce major cardiovascular outcomes and BP comparable to full doses of other classes,<sup>25,26</sup> 12.5 to 25.0 mg/d of hydrochlorothiazide have not been studied in a placebo-controlled outcome trial and have been shown to be inferior when combined with an angiotensin-converting enzyme inhibitor compared with full-dose amlodipine combined with an angiotensin-converting enzyme inhibitor.<sup>27</sup> In addition, the 12.5- to 25.0-mg/d hydrochlorothiazide dose has been reported in a meta-analysis to be less effective in reducing BP than full doses of other classes,<sup>28</sup> although 50 mg/d was comparable to other classes. Nevertheless, we evaluated 12.5 to 25.0 mg of hydrochlorothiazide in combination with olmesartan because this is the dose range available on the market for the olmesartan/hydrochlorothiazide FDC, as well as for all other currently marketed ARB-thiazide FDCs.

The greater efficacy of the azilsartan medoxomil/chlorthalidone FDC may also be driven by the azilsartan medoxomil component, given that it is associated with greater BP reduction than other ARBs.<sup>3–5</sup> The greater antihypertensive effect of azilsartan medoxomil may be explained in part by slower dissociation from the angiotensin type 1 receptor compared with other ARBs.<sup>29,30</sup>

### Limitations

Although this forced-titration design gives the most accurate reflection of true differences in the regimens being compared, it is different from the usual clinical practice of titrating medications to achieve a specified BP goal. A consequence of this design is that the BPs achieved are often lower than would be necessary to reach BP goals. In this trial, achieved SBP for all 3 of the groups averaged in the 120 to 130 mm Hg range. The lower levels of achieved BP may have exaggerated the elevations in creatinine observed, especially in the 80/25-mg azilsartan medoxomil/chlorthalidone group. Despite greater uric acid elevations in the azilsartan medoxomil/chlorthalidone groups compared with the olmesartan/hydrochlorothiazide group, reports of gout were infrequent and similar across groups; however, the relatively short study duration does not inform potential long-term differences.

### Perspectives

This large, forced-titration study comparing 2 ARB-diuretic FDCs demonstrated superior antihypertensive efficacy of 2 doses of azilsartan medoxomil/chlorthalidone compared with the maximum US Food and Drug Administration–approved dose of olmesartan/hydrochlorothiazide. Tolerability was relatively similar for the lower 40/25-mg dose of azilsartan medoxomil/chlorthalidone and olmesartan/hydrochlorothiazide FDC. There was a moderately higher adverse event discontinuation rate for the higher 80/25-mg dose of azilsartan medoxomil/chlorthalidone. In recognition of the comparable efficacy of the azilsartan medoxomil/chlorthalidone 40/25- and 80/25-mg doses but better tolerability of the 40/25-mg dose, the highest dose strength proposed by the

sponsor and approved by the US Food and Drug Administration is 40/25 mg.

Therefore, the FDC of azilsartan medoxomil/chlorthalidone 40/25-mg once daily provides a well-tolerated and more effective treatment for stage 2 systolic hypertension than olmesartan/hydrochlorothiazide 40/25 mg. The implication of these results is that this single-pill combination of 2 antihypertensive drugs may provide BP control to recommended target BP levels for a higher proportion of hypertensive patients than other 2-drug FDCs. Although some hypertensive patients will require more medications to achieve their BP goal, the subsequent regimen will likely require fewer additional drugs.

### Sources of Funding

This study was funded by Takeda Global Research and Development Center, Inc (Takeda).

### Disclosures

W.C.C. has received grant or research support from GlaxoSmith-Kline, Novartis, and Merck and is a consultant for Takeda, Novartis, Daiichi-Sankyo, and Astra Zeneca. G.L.B. has received grant or research support from Forest, Medtronic, and Relypsa and is a consultant for Takeda, Abbott, CVRx, Johnson & Johnson, Eli Lilly, Daiichi Sankyo, and the US Food and Drug Administration. He is a member of the speakers bureau for Takeda. W.B.W. has served as a paid consultant for Takeda. M.A.W. is a member of the speakers bureau and a consultant for Boehringer-Ingelheim, Daiichi Sankyo, Forest, Novartis, and Takeda. D.S. has a research or consultant relationship with Takeda, Novartis, and Boehringer-Ingelheim. A.R., E.L., and S.K. are full-time employees of Takeda.

### References

- Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA*. 2010;303:2043–2050.
- Takeda Pharmaceuticals America, Inc. Edarbi (azilsartan medoxomil) package insert. Deerfield, IL: Inc; 2011.
- White WB, Weber MA, Sica D, Bakris GL, Perez A, Cao C, Kupfer S. 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. *Hypertension*. 2011;57:413–420.
- Bakris GL, Sica D, Weber M, White WB, Roberts A, Perez A, Cao C, Kupfer S. The comparative effects of azilsartan medoxomil and olmesartan on ambulatory and clinic blood pressure. *J Clin Hypertens (Greenwich)*. 2011;13:81–88.
- Sica D, White WB, Weber MA, Bakris GL, Perez A, Cao C, Handley A, Kupfer S. Comparison of the novel angiotensin II receptor blocker azilsartan medoxomil vs valsartan by ambulatory blood pressure monitoring. *J Clin Hypertens (Greenwich)*. 2011;26:185–193.
- Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. *Hypertension*. 2011;57:689–694.
- Sica DA. Chlorthalidone: has it always been the best thiazide-type diuretic? *Hypertension*. 2006;47:321–322.
- Flack JM, Sica DA, Nesbitt S. Chlorthalidone versus hydrochlorothiazide as the preferred diuretic: is there a verdict yet? *Hypertension*. 2011;57:665–666.
- Hypertension Detection and Follow-Up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program: I—reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA*. 1979;242:2562–2571.
- SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;265:3255–3264.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981–2997. (Correction. 2004;291:2196, 2003;289:178.)
- Wright JT Jr, Probstfield JL, Cushman WC, Pressel SL, Cutler JA, Davis BR, Einhorn PT, Rahman M, Whelton PK, Ford CE, Haywood LJ, Margolis KL, Oparil S, Black HR, Alderman MH, for the ALLHAT Collaborative Research Group. ALLHAT findings revisited in the context of subsequent analyses, other trials, and meta-analyses. *Arch Intern Med*. 2009;169:832–842.
- Ernst ME, Carter BL, Goerdt CJ, Steffensmeier JGG, Phillips BB, Zimmerman MB, Bergus GR. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension*. 2006;47:352–358.
- Graves JW, Tibor M, Murtagh B, Klein L, Sheps SG. The Accoson Greenlight 300, the first non-automated mercury-free blood pressure measurement device to pass the International Protocol for blood pressure measuring devices in adults. *Blood Press Monit*. 2004;9:13–17.
- O'Brien E, Pickering T, Asmar R, Myers M, Parati G, Staessen J, Mengden T, Imai Y, Waeber B, Palatini P, Gerin W. Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. *Blood Press Monit*. 2002;7:3–17.
- Oparil S, Melino M, Lee J, Fernandez V, Heyrman R. Triple therapy with olmesartan medoxomil, amlodipine besylate, and hydrochlorothiazide in adult patients with hypertension: the TRINITY multicenter, randomized, double-blind, 12-week, parallel-group study. *Clin Ther*. 2010;32:1252–1269.
- Calhoun DA, Lacourcière Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. *Hypertension*. 2009;54:32–39.
- Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004;43(5 suppl 1):S1–S290.
- Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med*. 2000;160:685–693.
- Palmer BF. Renal dysfunction complicating the treatment of hypertension. *N Engl J Med*. 2002;347:1256–1261.
- Ram CV, Garrett BN, Kaplan NM. Moderate sodium restriction and various diuretics in the treatment of hypertension. *Arch Intern Med*. 1981;141:1015–1019.
- Izzo JL Jr, Weintraub H, Duprez D, Purkayastha D, Zappe D, Samuel R, Cushman WC. Treating systolic hypertension in the very elderly with valsartan-hydrochlorothiazide vs either monotherapy: ValVET primary results. *J Clin Hypertens (Greenwich)*. 2011;13:722–730.
- Neutel JM, Saunders E, Bakris GL, Cushman WC, Ferdinand KC, Ofili EO, Sowers JR, Weber MA, on behalf of the INCLUSIVE Investigators. The efficacy and safety of low- and high-dose fixed combinations of irbesartan/HCTZ in patients with uncontrolled systolic blood pressure on monotherapy: the INCLUSIVE Trial. *J Clin Hypertens (Greenwich)*. 2005;7:578–586.
- Izzo JL Jr, Neutel JM, Silfani T, Dubiel R, Walker F. Efficacy and safety of treating stage 2 systolic hypertension with olmesartan and olmesartan/HCTZ: results of an open-label titration study. *J Clin Hypertens (Greenwich)*. 2007;9:36–44.
- Materson BJ, Reda DJ, Cushman WC, Massie BM, Freis ED, Kochar MS, Hamburger RJ, Fye C, Lakshman R, Gottdiener J, Ramirez EA, Henderson WG, for the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Single-drug therapy for hypertension in men: a comparison of six antihypertensive agents with placebo. *N Engl J Med*. 1993;328:914–921.
- Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA*. 2003;289:2534–2544.
- Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, Hester A, Gupta J, Gatlin M, Velazquez EJ, on behalf of the ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417–2428.
- Messerli FH, Makani H, Benjo A, Romero J, Alviar C, Bangalore S. Antihypertensive efficacy of hydrochlorothiazide as evaluated by



ambulatory blood pressure monitoring: a meta-analysis of randomized trials. *J Am Coll Cardiol*. 2011;57:590–600.

29. Ojima M, Igata H, Tanaka M, Sakamoto H, Kuroita T, Kohara Y, Kubo K, Fuse H, Imura Y, Kusumoto K, Nagaya H. In vitro antagonistic properties of a new angiotensin type 1 receptor blocker, azilsartan, in

receptor binding and function studies. *J Pharmacol Exp Ther*. 2011;336:801–808.

30. Kajiya T, Ho C, Wang J, Vilardi R, Kurtz TW. Molecular and cellular effects of azilsartan: a new generation angiotensin II receptor blocker. *J Hypertens*. 2011;29:2476–2483.

### Novelty and Significance

#### What Is New?

- This was the first forced-titration comparison of equal doses of chlorthalidone and hydrochlorothiazide in combination with angiotensin receptor blockers.

#### What Is Relevant?

- Combination azilsartan medoxomil 40 or 80 mg/chlorthalidone 25 mg significantly reduced clinic systolic blood pressure by 5 to 7 mm Hg more than combination olmesartan 40 mg/hydrochlorothiazide 25 mg.

- Combination azilsartan medoxomil/chlorthalidone significantly reduced ambulatory blood pressure more than combination olmesartan/hydrochlorothiazide during every hour of the interdosing interval.

#### Summary

Combination azilsartan medoxomil/chlorthalidone resulted in superior blood pressure reduction compared with combination olmesartan/hydrochlorothiazide in patients with stage 2 hypertension.

## ONLINE SUPPLEMENT

# **AZILSARTAN MEDOXOMIL PLUS CHLORTHALIDONE REDUCES BLOOD PRESSURE MORE EFFECTIVELY THAN OLMESARTAN PLUS HYDROCHLOROTHIAZIDE IN STAGE 2 SYSTOLIC HYPERTENSION**

William C. Cushman<sup>1</sup>, George L. Bakris<sup>2</sup>, William B. White<sup>3</sup>, Michael A. Weber<sup>4</sup>,  
Domenic Sica<sup>5</sup>, Andrew Roberts<sup>6</sup>, Eric Lloyd<sup>6</sup>, Stuart Kupfer<sup>6</sup>

<sup>1</sup>University of Tennessee College of Medicine, Memphis, TN

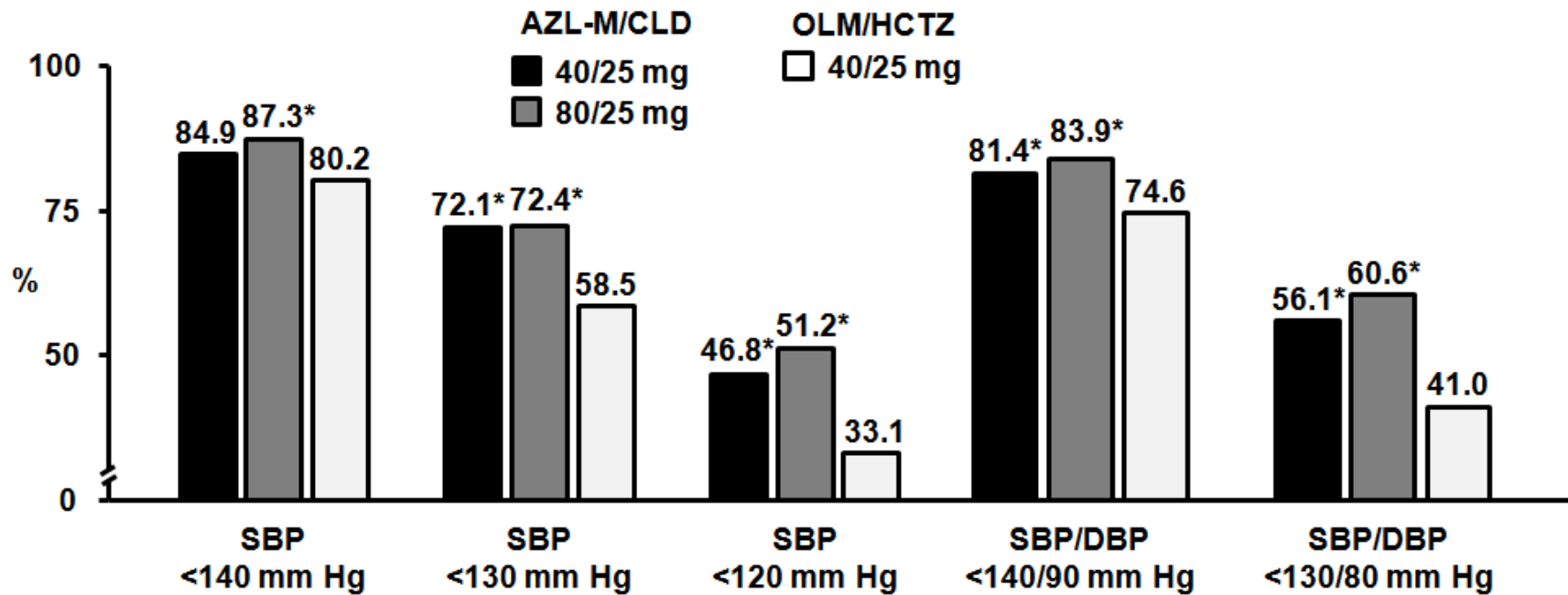
<sup>2</sup>University of Chicago Pritzker School of Medicine, Chicago, IL

<sup>3</sup>University of Connecticut School of Medicine, Farmington, CT

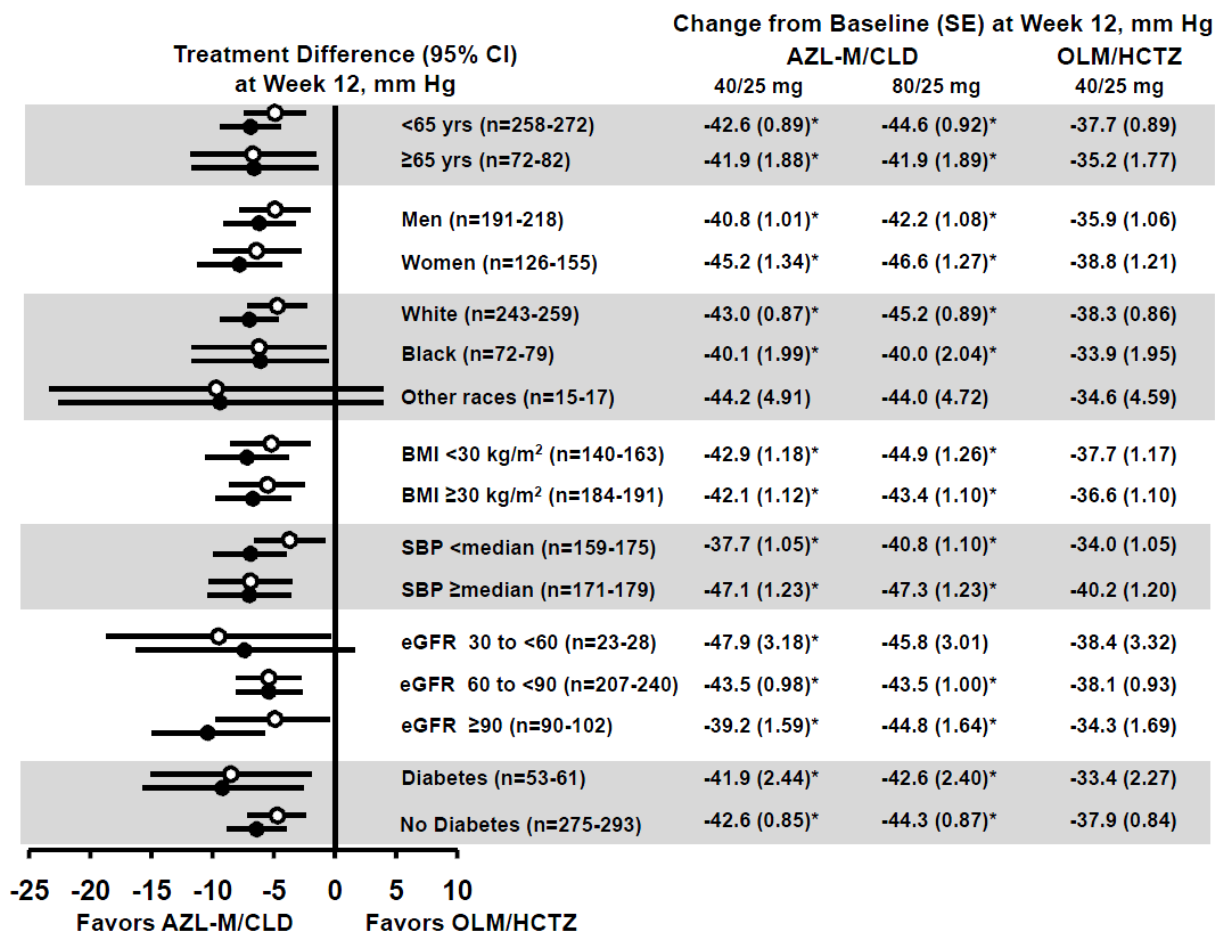
<sup>4</sup>Downstate Medical Center, Brooklyn, NY

<sup>5</sup>Virginia Commonwealth University, Richmond, VA

<sup>6</sup>Takeda Global Research and Development Center, Inc., Deerfield, IL



**Figure S1.** Percent of subjects who reached categorical BP targets at week 12. AZL-M/CLD = azilsartan medoxomil/chlorthalidone, OLM/HCTZ = olmesartan/ hydrochlorothiazide. \*P<0.05 for the odds ratios (not shown) between each AZL-M/CLD group and the OLM/HCTZ group.



**Figure S2.** Subgroup analyses of clinic SBP by baseline characteristics. AZL-M/CLD = azilsartan-medoxomil/chlorthalidone, OLM/HCTZ = olmesartan/hydrochlorothiazide. Open circles (○) are treatment differences between AZL-M/CLD 40/25 mg and OLM/HCTZ. Closed circles (●) are the treatment differences between AZL-M/CLD 80/25 mg group and OLM/HCTZ. The median clinic SBP at baseline was 163.3 mm Hg. Baseline eGFR categories expressed as ml/min/1.73 m<sup>2</sup>. \*P<0.05 vs. OLM/HCT.

**Azilsartan Medoxomil Plus Chlorthalidone Reduces Blood Pressure More Effectively Than Olmesartan Plus Hydrochlorothiazide in Stage 2 Systolic Hypertension**  
William C. Cushman, George L. Bakris, William B. White, Michael A. Weber, Domenic Sica, Andrew Roberts, Eric Lloyd and Stuart Kupfer

*Hypertension*. 2012;60:310-318; originally published online June 18, 2012;  
doi: 10.1161/HYPERTENSIONAHA.111.188284

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
Copyright © 2012 American Heart Association, Inc. All rights reserved.  
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hyper.ahajournals.org/content/60/2/310>

Data Supplement (unedited) at:

<http://hyper.ahajournals.org/content/suppl/2012/06/18/HYPERTENSIONAHA.111.188284.DC1.html>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:  
<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Hypertension* is online at:  
<http://hyper.ahajournals.org/subscriptions/>