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Evaluation of efficacy and safety of fixed- dose combinations of azilsartan medoxomil/ chlorthalidone vs olmesartan medoxomil/hydrochlorothiazide

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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 71 participants with baseline clinic systolic blood pressure 160 to 190 mm Hg and diastolic blood pressure <119 mm Hg. Patients had a mean age of 57 years; 59% were men. 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±SE) were 42.5±0.8, 44.0±0.8, and 37.1±0.8 mm Hg, respectively. Changes in 24-hour ambulatory systolic blood pressure were 33.9±0.8, 36.3±0.8, and 27.5±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 forced-titration study has demonstrated superior antihypertensive efficacy of azilsartan medoxomil/chlorthalidone fixed-dose combinations compared with the maximum approved dose of olmesartan/hydrochlorothiazide.

Keywords: azilsartan medoxomil, chlorthalidone, olmesartan medoxomil, hydrochlorothiazide

Introduction
Although control of hypertension in the India 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 [1]. 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 bio-availability of 60% and elimination half-life of 12 hours [2]. At its maximal dose, azilsartan medoxomil has superior efficacy compared with both olmesartan and valsartan at their maximum, approved doses, without increasing adverse events [3–5]. Chlorthalidone is a potent, long-acting thiazide-like diuretic that has a strong evidence base supporting cardiovascular benefit from randomized, controlled clinical trials [6–12]. It is also more effective in lowering BP than the more commonly used thiazide diuretic, hydrochlorothiazide [13]. Therefore, combinations of azilsartan medoxomil and chlorthalidone are being developed as an effective 2-drug FDC.

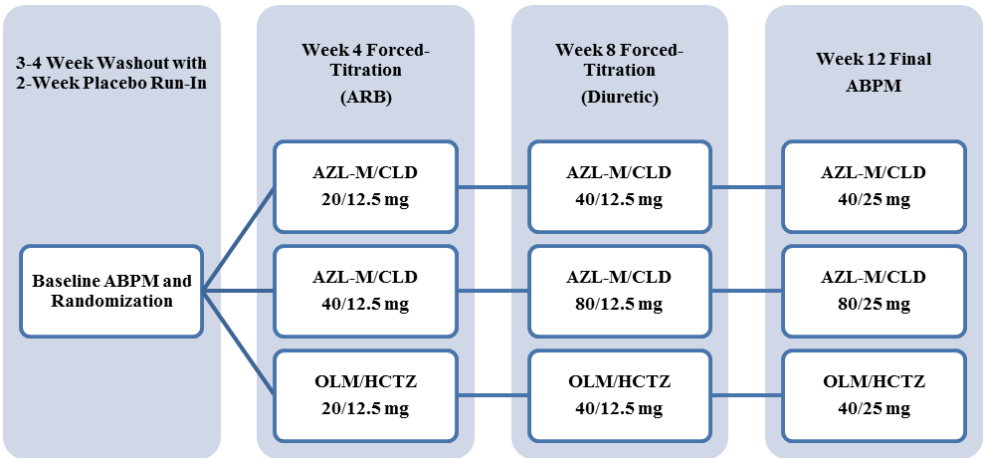

Fig 1: Treatments and titration schedule. AZL-M/CLD indicates azilsartan medoxomil/chlorthali-done; OLM/HCTZ, olmesartan/ hydrochlorothiazide; ABPM, ambulatory blood pressure monitoring.

The present 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 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 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. 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).

Patients

Men and women who were ~18 years of age and had primary hypertension were recruited from Hi-Tech Medical College and Hospital, Bhubaneswar. 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 m2); known or suspected renal artery stenosis; clinically relevant or unstable cardiovascular diseases within 6 months of enrolment; 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.

BP and Assessments

Clinic BP was measured at baseline and each post randomization visit (weeks 2, 4, 8, 10, and 12) using a manual sphygmomanometer.[14] 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)*15 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 non-consecutive 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 non-evaluable.

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 non-serious or serious and whether it resulted in discontinuation of treatment. In addition, investigator was 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 magnesium), and metabolic function (serum uric acid, glucose, and fasting lipids).

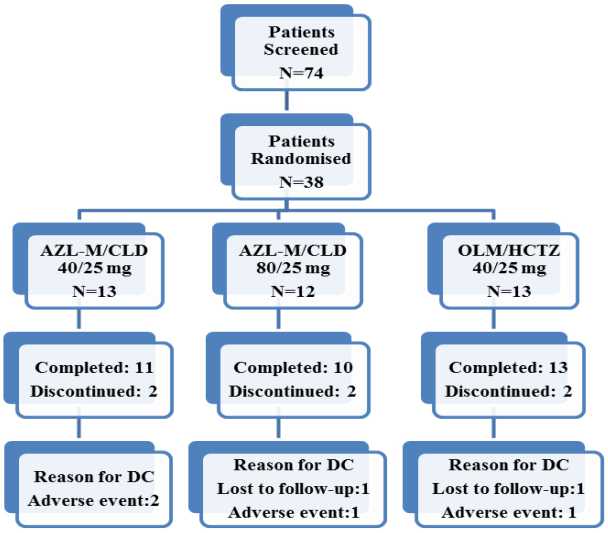

Fig 2: Patient disposition. Data are n (%). DC indicates discontinuation; AZL-M/ CLD, azilsartan medoxomil/chlorthalidone; OLM/ HCTZ, olmesartan/hydrochlorothiazide.

Statistical Analyses

End Points

The primary end point was change from baseline in trough (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 endpoint 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 endpoints 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 per-formed for each end point by age (<65 years or ~65 years), sex. 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 38 randomized subjects (12 per group) was determined as sufficient to achieve ~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 74 patients screened, 52 (71%) were enrolled in the placebo run-in period, and of these 38 (51%) met the entry criteria and were randomized. Participants were randomized to 1 of 3 active treatment groups (12-13 per group); 32 (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. Across treatment groups, mean trough clinic BP was 165/96 mm Hg.

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;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/chlorthali-done 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. 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).

Table 1: Demographic and Baseline Characteristics

Characteristics	AZL-M/CLD 40/25 mg (N=13)	AZL-M/CLD 80/25 mg (N=12)	OLM/HCTZ 40/25 mg (N=13)
Sex, n (%)			
Male	8 (62.8)	7 (57.1)	7 (56.3)
Female	5 (37.2)	5 (42.9)	6 (43.7)
Age, y, mean (SD)	56.4 (10.5)	56.7 (10.1)	56.7 (10.9)
Race, n (%)			
Asian	13 (100)	12 (100)	13 (100)
Prior use of antihypertensive therapy, n (%)	10 (76.9)	9 (79.8)	9 (76.1)
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.

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

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.

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. There was no statistical evidence that the treatment differences were dependent on age, sex, race, baseline hypertension severity (P>0.10).

Table 2: Change from Baseline in Clinic Blood Pressure and Through 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	13	12	13	13	12	13
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	11	10	11	11	10	11
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	11	10	11	11	10	11
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 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 non-progressive and associated with relatively large BP and weight reductions. For patients with elevations of serum creatinine 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.

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	13	12	13
Any AE	9 (71.3)	8 (70.7)	8 (60.2)
Most common AEs			
Blood creatinine increased	-	-	
Dizziness	2	2	2
Fatigue	2	2	1
Headache	2	1	2
Blood uric acid increased	1	1	1
AEs leading to discontinuation	2	2	2
Dizziness	1	-	-
Blood creatinine increased	-	-	1
Hypotension	1	1	1
Serious AEs	-	-	-
Serum laboratory parameters of interest†			
Creatinine: ≥ 2 consecutive elevations (≥ 1.5 x baseline and > ULN)		1/12 (4.4)	

Data are n (%). AZL-M indicates azilsartan-medoxomil/chlorthalidone; OLM/HCTZ, olmesartan/hydrochlorothiazide; AE, adverse event; 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.

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

Discussion

This 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/hydro-chlorothiazide 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 [16, 17]. Reductions of clinic SBP were consistently greater in both azilsartan medoxomil/chlorthalidone groups compared with olmesartan/hydrochlorothiazide.

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 40mm Hg or more above this level.[18] The mechanism for this fall is in part related to a reduction in intra-glomerular pressure secondary to dilation of the efferent arteriole in each glomerulus and reduced systemic pressure transmission at the afferent arteriole.[18,19] Patients with chronic hypertension and subsequent endothelial dysfunction may be more susceptible to this phenomenon because of less effective autoregulation of renal blood flow.[20] 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 auto-regulation 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 [21]. 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 [22], maximum dose 320/25 mg, in men and women ~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 [23]. 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 ~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 [24].

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 azilasartan medoxomil component, given that it is associated with greater BP reduction than other ARBs [3–5]. 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 [25, 26].

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 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 and 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 approved by the 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.

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