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


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 ≥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±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 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.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 bioavailability 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.

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...
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) >130 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 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/deflation rate (Greenlight 300 sphygmomanometer; Accoson, Harlow, United Kingdom). 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) 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
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 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, an SD of 14 mm Hg, and a 15% dropout 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;
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 20/25 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).

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Table 1. Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AZL-M/CLD 40/25 mg (N=355)</th>
<th>AZL-M/CLD 80/25 mg (N=352)</th>
<th>OLM/HCTZ 40/25 mg (N=364)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>223 (62.8)</td>
<td>201 (57.1)</td>
<td>205 (56.3)</td>
</tr>
<tr>
<td>Female</td>
<td>132 (37.2)</td>
<td>151 (42.9)</td>
<td>159 (43.7)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>56.4 (10.5)</td>
<td>56.7 (10.1)</td>
<td>56.7 (10.9)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>2 (0.6)</td>
<td>5 (1.4)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Asian</td>
<td>13 (3.7)</td>
<td>11 (3.1)</td>
<td>11 (3.0)</td>
</tr>
<tr>
<td>Black</td>
<td>80 (22.5)</td>
<td>80 (22.7)</td>
<td>80 (22.0)</td>
</tr>
<tr>
<td>White</td>
<td>261 (73.5)</td>
<td>258 (73.3)</td>
<td>267 (73.4)</td>
</tr>
<tr>
<td>Prior use of antihypertensive therapy, n (%)</td>
<td>273 (76.9)</td>
<td>281 (79.8)</td>
<td>277 (76.1)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>54 (15.2)</td>
<td>59 (16.8)</td>
<td>65 (17.9)</td>
</tr>
<tr>
<td>eGFR, n (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30 to &lt;60 mL/min per 1.73 m²</td>
<td>26 (7.3)</td>
<td>29 (8.2)</td>
<td>25 (6.9)</td>
</tr>
<tr>
<td>≥60 to &lt;90 mL/min per 1.73 m²</td>
<td>224 (63.1)</td>
<td>220 (62.5)</td>
<td>246 (67.6)</td>
</tr>
<tr>
<td>≥90 mL/min per 1.73 m²</td>
<td>105 (29.6)</td>
<td>103 (29.3)</td>
<td>91 (25.0)</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>31.4 (5.94)</td>
<td>31.9 (6.59)</td>
<td>31.6 (5.92)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic SBP/DBP</td>
<td>164.9 (10.1)/96.1 (9.8)</td>
<td>164.8 (10.4)/95.9 (9.8)</td>
<td>164.7 (9.9)/95.2 (10.3)</td>
</tr>
<tr>
<td>Trough BP‡ SBP/DBP</td>
<td>153.0 (16.8)/92.5 (12.5)</td>
<td>154.5 (16.8)/92.4 (12.1)</td>
<td>152.8 (16.5)/91.5 (12.2)</td>
</tr>
<tr>
<td>24-h mean SBP/DBP</td>
<td>149.3 (13.6)/88.1 (10.9)</td>
<td>150.8 (13.8)/88.4 (10.9)</td>
<td>149.2 (14.0)/87.1 (11.0)</td>
</tr>
</tbody>
</table>

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.

‡Data were measured during the last 2 hours of the ambulatory BP recording.
Table 2. Change From Baseline in Clinic Blood Pressure and Trough and 24-h Mean Blood Pressure by ABPM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AZL-M/CLD 40/25 mg</th>
<th>AZL-M/CLD 80/25 mg</th>
<th>OLM/HCTZ 40/25 mg</th>
<th>AZL-M/CLD 40/25 mg</th>
<th>AZL-M/CLD 80/25 mg</th>
<th>OLM-M/HCTZ 40/25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>344</td>
<td>330</td>
<td>354</td>
<td>344</td>
<td>330</td>
<td>354</td>
</tr>
<tr>
<td>Baseline</td>
<td>164.8±0.5</td>
<td>165.0±0.6</td>
<td>164.6±0.5</td>
<td>96.1±0.5</td>
<td>95.9±0.6</td>
<td>95.3±0.5</td>
</tr>
<tr>
<td>Change at wk 4</td>
<td>-34.7±0.8</td>
<td>-36.7±0.8</td>
<td>-29.7±0.8</td>
<td>-14.9±0.5</td>
<td>-15.8±0.5</td>
<td>-11.7±0.5</td>
</tr>
<tr>
<td>Change at wk 8</td>
<td>-39.1±0.8</td>
<td>-39.4±0.8</td>
<td>-35.3±0.8</td>
<td>-17.0±0.5</td>
<td>-17.7±0.5</td>
<td>-13.9±0.5</td>
</tr>
<tr>
<td>Change at wk 12</td>
<td>-42.5±0.8</td>
<td>-44.0±0.8</td>
<td>-37.1±0.8</td>
<td>-18.8±0.5</td>
<td>-20.5±0.5</td>
<td>-16.4±0.5</td>
</tr>
<tr>
<td>Difference†</td>
<td>-5.3 (-7.6 to -3.1)</td>
<td>-6.9 (-9.2 to -4.6)</td>
<td>...</td>
<td>-2.3 (-3.6 to -1.0)</td>
<td>-4.1 (-5.4 to -2.8)</td>
<td>...</td>
</tr>
</tbody>
</table>

| 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)| ...               |

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).

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 nonprogressive 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.

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). 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. 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. 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. Patients with chronic hypertension and subsequent endothelial dysfunction may be more susceptible to this phenomenon because of less effective autoregulation of renal blood flow. 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, 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, 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, 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.

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. 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. 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, 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. 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, 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. 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.

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.

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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/chlorthalidone 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.
Azilsartan Medoxomil Plus Chlorthalidone Reduces Blood Pressure More Effectively Than Olmesartan Plus Hydrochlorothiazide in Stage 2 Systolic Hypertension
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AZILSARTAN MEDOXOMIL PLUS CHLORTHALIDONE REDUCES BLOOD PRESSURE MORE EFFECTIVELY THAN OLMESARTAN PLUS HYDROCHLOROTHIAZIDE IN STAGE 2 SYSTOLIC HYPERTENSION

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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 m². *P<0.05 vs. OLM/HCT.