Original Paper

Efficacy and Safety of Treating Stage 2 Systolic Hypertension With Olmesartan and Olmesartan/HCTZ: Results of an Open-Label Titration Study

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This study investigated an aggressive treatment program for stage 2 systolic hypertension (pretreatment systolic blood pressure [SBP] ≥160 mm Hg) using the angiotensin receptor blocker olmesartan medoxomil (OM) and hydrochlorothiazide (HCTZ). In this open-label, 16-week trial, 170 subjects received OM 20 mg/d for 3 weeks. If seated SBP/diastolic BP remained ≥120/80 mm Hg, subjects were advanced to successive 3-week courses of OM 40 mg/d, OM/HCTZ 40/12.5 mg/d, and OM/HCTZ 40/25 mg/d. OM 20 mg/d reduced mean SBP by 16.9 mm Hg (P<.001), and there were further dose-dependent decreases in mean SBP to a maximum of 34.5 mm Hg with OM/HCTZ 40/25 mg/d. At study end, 75.1% of subjects achieved SBP goal (<140 mm Hg) and 16.0% achieved SBP normalization (<120 mm Hg). Treatment was well tolerated at all doses. The addition of HCTZ did not change serum potassium levels but resulted in a dose-independent but not symptomatic increase in serum glucose and uric acid. The authors conclude that an OM-based regimen, with or without HCTZ in conventional doses, is effective in controlling and normalizing BP in stage 2 systolic hypertension. (J Clin Hypertens. 2007;9:36–44) ©2007 Le Jacq

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Systolic blood pressure (SBP) is a better predictor of major cardiovascular adverse events than is diastolic blood pressure (DBP), particularly in older individuals.[1–3] In the National Health and Nutrition Examination Survey (NHANES),[2] approximately two thirds of hypertensive individuals older than 60 years had isolated systolic hypertension (ISH). Historically, SBP control has been difficult to achieve, even when aggressively managed under clinical trial conditions,[4–6] and 2 or more antihypertensive agents are needed in most cases.[7,8] Indeed, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[7] recommended combination therapy as initial treatment in patients with stage 2 systolic hypertension (SBP ≥160 mm Hg). Optimal efficiency of 2-drug combinations requires that the agents be chosen from different drug classes with complementary mechanisms of action[7,8] (eg, diuretics and angiotensin II receptor blockers [ARBs]).

ARBs are effective in reducing SBP[9] and demonstrate a tolerability profile similar to placebo even at higher doses.[10–12] Furthermore, combining lower doses of hydrochlorothiazide (HCTZ) with an ARB lowers blood pressure (BP) more effectively than higher doses of either agent alone.[13–16] For the past

decade, several ARBs have been combined with low-dose (12.5 mg/d) HCTZ; these combinations are safe and effective.[17,18] More recent studies have demonstrated that increasing the HCTZ dosage to 25 mg/d reduces BP further.[16] In addition to increased BP-lowering efficacy, the coadministration of an ARB or an angiotensin-converting enzyme inhibitor (ACEI) with a thiazide diuretic may also help offset some of the potential adverse events associated with diuretic therapy,[13,14,16,19,20] including hypokalemia and serum uric acid elevations.[18,21–23]

This open-label study in subjects with stage 2 systolic hypertension assessed the efficacy and safety of a treatment algorithm that included the ARB olmesartan medoxomil (OM) combined with HCTZ. The primary end point was the mean change from baseline in SBP at 12 weeks. Secondary end points included the percentage of subjects who attained BP goal (<140/90 mm Hg) and full BP normalization (<120/80 mm Hg).

METHODS

Study Design and Subjects

This prospective, open-label, multicenter titration study consisted of four 3-week treatment periods. At the initial screening, subjects discontinued all antihypertensive medications and entered into a single-blind placebo run-in period of 3–4 weeks. All subjects who qualified for the active treatment phase began therapy with OM 20 mg/d.

Subjects visited the clinic every 3 weeks. At each visit, antihypertensive therapy was up-titrated using a stepwise algorithm from OM 20 mg to 40 mg, then adding HCTZ first at 12.5 mg/d and then 25 mg/d until BP normalized to <120/80 mm Hg. Subjects were instructed to take all study medication once daily at 8 AM ± 2 hours. Subjects exited the study at any clinic visit during the active treatment phase once they achieved normalized BP.

Men and women 18 years and older with stage 2 systolic hypertension were eligible for enrollment if they had a mean seated SBP ≥160 mm Hg and <200 mm Hg and a mean seated DBP <110 mm Hg at 2 consecutive qualifying visits during the placebo run-in period, and the difference between these 2 SBP measurements was ≤15 mm Hg. To exclude white coat hypertension, subjects who qualified on the basis of clinic BP underwent 8-hour (8 AM–4 PM) ambulatory BP monitoring at the end of the placebo run-in and were required to have a mean 8-hour daytime ambulatory SBP >140 mm Hg and ≤180 mm Hg and DBP <110 mm Hg.

Exclusion criteria included hypertensive encephalopathy, stroke, or transient ischemic attack; or a history of myocardial infarction, percutaneous transluminal coronary revascularization, coronary artery bypass graft, and/or unstable angina pectoris within the past 6 months; documented congestive heart failure; type 1 diabetes mellitus (subjects with type 2 diabetes controlled with diet or oral hypoglycemic agents were included, provided the dose of these agents had been stable for at least 1 month before the placebo run-in period); and pregnancy or lactation.

If at any time SBP was >200 mm Hg or DBP was >110 mm Hg, the subject was removed from the study and treated with other antihypertensive therapy.

Table I. Demographics and Baseline Characteristics of the Efficacy Cohort (N=169)

Age, mean (range), y	60.1 (33–84)
Race, No. (%)	
White	124 (73.4)
Black	26 (15.4)
Asian	4 (2.4)
Hispanic	13 (7.7)
Other	2 (1.2)
Sex, No. (%)	
Men	78 (46.2)
Women	91 (53.8)
Baseline SBP/DBP, mean, mm Hg*	171.4/95.2

*Average of the 2 means of the last 2 weeks of the placebo run-in period. SBP indicates seated systolic blood pressure (BP); DBP, seated diastolic BP.

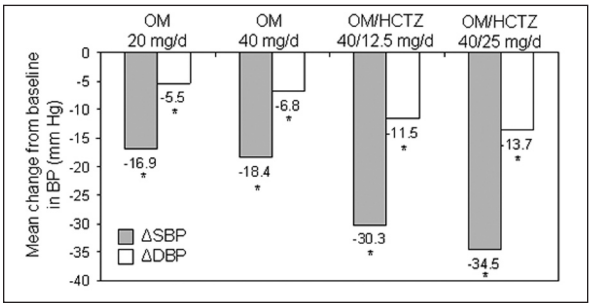

*Figure 1. Reduction from baseline in mean seated systolic BP (ΔSBP) and mean seated diastolic BP (ΔDBP). *P<.001 vs baseline. Blood pressure (BP) reductions are calculated using the last-observation-carried-forward method for subjects who exited the study during a treatment period after having taken at least 1 dose of the study drug for that period. Therefore, mean BP reductions are based on the n value shown for that dose/step of the treatment algorithm. OM indicates olmesartan medoxomil; HCTZ, hydrochlorothiazide.*

Efficacy and Safety Assessments

Seated BP was measured at each visit before subjects took their daily dose of study medication. Measurements were obtained after a 5-minute

Table II. Efficacy of Olmesartan Medoxomil (OM) and OM/HCTZ in the Total Patient Population (Efficacy Cohort)

	Week/Treatment			
Efficacy Measure, mm Hg	3/OM 20 mg/d (N=169)	6/OM 40 mg/d (N=160)	9/OM/HCTZ 40/12.5 mg/d (N=157)	12/OM/HCTZ 40/25 mg/d (N=143)
Baseline SBP/DBP, mean	171.4/95.2	171.3/95.4	171.4/95.4	171.4/95.7
ΔSBP, mean (SD)*	–16.9 (14.3)†	–18.4 (15.3)†	–30.3 (15.0)†	–34.5 (14.4)†
ΔDBP, mean (SD)*	–5.5 (8.4)†	–6.8 (7.7)†	–11.5 (9.1)†	–13.7 (8.9)†
BP <140/90, %‡	15.4	29.0	55.6	70.4
BP <120/80, %‡	1.2	1.2	5.9	15.4

*Last observation carried forward. †P<.001 vs baseline. ‡Cumulative (percentage of the total number of patients in the efficacy cohort). HCTZ indicates hydrochlorothiazide; SBP, systolic blood pressure (BP); DBP, diastolic BP; and Δ, change.

seated rest period using an Omron BP monitor model HEM-705CP (Omron Healthcare Inc, Bannockburn, IL) at all sites, validated for accuracy. The determination of proper BP cuff length/width and positioning of the cuff on the dominant arm of each subject were performed in accordance with the study protocol at all sites. Three measurements separated by 2-minute intervals were obtained, and the mean was used as the BP value for that visit.

The primary efficacy variable was the change in SBP from baseline after 12 weeks of treatment. Secondary efficacy variables included the change from baseline in SBP and DBP at the end of each treatment period, the percentage of subjects who achieved SBP goal (SBP <140 mm Hg) and BP goal (<140/90 mm Hg), and the percentage of subjects who achieved SBP normalization (<120 mm Hg) and BP normalization (<120/80 mm Hg).

The efficacy cohort included all subjects who received at least 1 dose of study medication and had a baseline measurement and at least 1 efficacy measurement after taking the study medication.

Secondary (post hoc) analyses were conducted to determine the efficacy of treatment in several subpopulations of subjects: elderly (65 years and older) and nonelderly (younger than 65 years); ISH; black and nonblack; men and women; and body mass index (BMI) of <25 kg/m^2 (normal), 25–29 kg/m^2 (overweight), and ≥30 kg/m^2 (obese).

Subjects were evaluated for medication compliance and for the occurrence of any clinical adverse events, laboratory adverse events, and changes in physical examination findings, vital signs, or electrocardiogram (ECG) findings. Laboratory tests included standard hematology, serum β-human chorionic gonadotropin, serum chemistry, and blood chemistry panel. The safety cohort included all subjects who received at least 1 dose of study medication.

Statistical Methods

The sample size was not based on statistical considerations. The planned enrollment of 110 subjects was considered sufficient to provide a reliable evaluation of treatment effect at the study end. Within-group comparisons between baseline and end of treatment were performed using paired t tests. If a subject dropped out of the study, the subject's last BP measurement taken during that treatment period (after the subject had taken at least 1 dose of the study drug) was carried forward as the final measurement for that period. The number and percentage of subjects reaching various BP goals were summarized for each titration period, as well as the cumulative proportion. Statistical comparisons between each treatment step were not conducted.

RESULTS

A total of 170 subjects were enrolled and formed the safety cohort; the efficacy cohort consisted of 169 subjects. During the study, 26 subjects achieved BP normalization and discontinued per protocol. A further 29 subjects discontinued during active treatment (11 because of an adverse event, 4 at their own request, and 14 for other reasons).

Demographics and Baseline Characteristics

The demographics of the efficacy cohort at baseline are presented in Table I. Mean baseline BP was 171/95 mm Hg, mean age was 60 years, 52% were 60 years or older, 46% were men, and 85% were nonblack.

Efficacy

BP Changes. OM alone and in combination with HCTZ significantly reduced both mean SBP and DBP (Table II, Figure 1) from baseline (P<.001). These BP reductions were dose dependent, ranging from –16.9/–5.5 mm Hg with OM 20 mg/d to –18.4/–6.8 mm Hg with OM 40 mg/d, –30.3/–11.5 mm Hg with OM/HCTZ 40/12.5 mg/d, and –34.5/–13.7 mm Hg with OM/HCTZ 40/25 mg/d.

Seated BP Goal and Normalization. The BP goal of <140/90 mm Hg was achieved in 26 of 169 subjects (15.4%) with OM 20-mg/d monotherapy

Table III. Efficacy of Olmesartan Medoxomil (OM) and OM/HCTZ in Subpopulations of Patients Based on the Results of a Post Hoc Analysis

Subpopulation/Efficacy Measure, mm Hg	OM 20 mg/d	OM 40 mg/d	OM/HCTZ 40/12.5 mg/d	OM/HCTZ 40/25 mg/d
Age				
<65 y, No.	109	104	101	93
Baseline SBP/DBP, mean	169.5/97.4	169.5/97.4	169.4/97.4	169.5/97.4
ΔSBP, mean (SD)*	–17.7 (14.7)†	–19.0 (15.6)†	–31.3 (14.9)†	–33.2 (13.9)†
ΔDBP, mean (SD)*	–6.5 (8.1)†	–7.3 (8.1)†	–13.0 (9.0)†	–14.0 (9.0)†
BP <140/90, %‡	17.4	33.9	61.5	75.2
≥65 y, No.	60	56	56	50
Baseline SBP/DBP, mean	174.7/91.0	174.7/91.6	174.9/91.8	174.9/92.7
ΔSBP, mean (SD)*	–15.5 (13.6)†	–17.2 (14.7)†	–28.7 (15.1)†	–37.0 (15.2)†
ΔDBP, mean (SD)*	–3.7 (8.7)§	–5.9 (6.8)†	–8.8 (8.5)†	–13.1 (8.8)†
BP <140/90, %‡	11.7	20.0	45.0	61.7
ISH				
ISH, No.	41	37	37	32
Baseline SBP, mean	173.1	173.0	173.3	172.9
ΔSBP, mean (SD)*	–17.7 (16.0)†	–17.7 (15.0)†	–29.6 (14.8)†	–36.4 (13.7)†
SBP <140, %‡	17.1	26.8	56.1	68.3
Non-ISH, No.	128	123	120	111
Baseline SBP, mean	170.8	170.8	170.8	170.9
ΔSBP, mean (SD)*	–16.6 (13.8)†	–18.6 (15.4)†	–30.6 (15.1)†	–34.0 (14.6)†
SBP <140, %‡	18.0	32.0	58.6	77.3
Race				
Nonblack, No.	143	134	131	118
Baseline SBP/DBP, mean	171.4/94.4	171.3/94.6	171.4/94.6	171.4/95.0
ΔSBP, mean (SD)*	–18.3 (13.9)†	–20.2 (13.8)†	–30.5 (15.2)†	–35.1 (14.6)†
ΔDBP, mean (SD)*	–5.9 (8.5)†	–7.3 (7.4)†	–11.2 (9.3)†	–13.7 (8.5)†
BP <140/90, %‡	16.8	30.8	55.9	72.7
Black, No.	26	26	26	25
Baseline SBP/DBP, mean	171.3/99.4	171.3/99.4	171.3/99.4	171.3/99.1
ΔSBP, mean (SD)*	–9.0 (14.0)‖	–9.0 (18.8)¶	–29.4 (14.1)†	–32.0 (13.5)†
ΔDBP, mean (SD)*	–3.5 (7.7)¶	–4.3 (8.6)¶	–13.0 (7.9)†	–13.4 (10.8)†
BP <140/90, %‡	7.7	19.2	53.8	57.7
Sex				
Men, No.	78	75	75	65
Baseline SBP/DBP, mean	170.8/96.7	170.9/96.8	170.9/96.8	171.4/97.2
ΔSBP, mean (SD)*	–15.9 (14.0)†	–20.3 (13.2)†	–29.0 (14.6)†	–32.2 (14.1)†
ΔDBP, mean (SD)*	–6.6 (8.0)†	–8.7 (7.1)†	–12.4 (8.5)†	–13.9 (8.1)†
BP <140/90, %‡	12.8	26.9	53.8	71.8
Women, No.	91	85	82	78
Baseline SBP/DBP, mean	171.8/93.9	171.7/94.2	171.8/94.1	171.3/94.5
ΔSBP, mean (SD)*	–17.7 (14.6)†	–16.7 (16.8)†	–31.6 (15.3)†	–36.5 (14.4)†
ΔDBP, mean (SD)*	–4.6 (8.7)†	–5.2 (7.8)†	–10.6 (9.5)†	–13.5 (9.6)†
BP <140/90, %‡	17.6	30.8	57.1	69.2
BMI				
<25 kg/m^2, No.	21	19	18	15
Baseline SBP/DBP, mean	172.5/92.9	172.7/92.3	173.1/91.8	172.4/93.9
ΔSBP, mean (SD)*	–17.0 (14.4)†	–17.5 (17.3)†	–29.2 (18.4)†	–31.3 (16.1)†
ΔDBP, mean (SD)*	–6.7 (8.1)†	–6.1 (9.6)¶	–10.0 (12.7)¶	–12.8 (12.1)†
BP <140/90, %‡	19.0	23.8	57.1	66.7

Table III. Efficacy of Olmesartan Medoxomil (OM) and OM/HCTZ in Subpopulations of Patients Based on the Results of a Post Hoc Analysis *(continued)*

Subpopulation/Efficacy Measure, mm Hg	OM 20 mg/d	OM 40 mg/d	OM/HCTZ 40/12.5 mg/d	OM/HCTZ 40/25 mg/d
BMI				
25–29 kg/m^2, No.	61	56	56	54
Baseline SBP/DBP, mean	171.5/94.6	171.2/95.4	171.2/95.4	171.3/95.1
ΔSBP, mean (SD)*	−17.0 (14.4)†	−19.8 (14.6)†	−29.4 (15.6)†	−36.6 (14.0)†
ΔDBP, mean (SD)*	−5.4 (8.2)†	−7.0 (7.0)†	−11.8 (9.3)†	−14.5 (7.3)†
BP <140/90, %‡	16.4	31.1	55.7	72.1
≥30 kg/m^2, No.	86	84	82	73
Baseline SBP/DBP, mean	171.0/96.0	171.1/96.0	171.1/96.1	171.2/96.4
ΔSBP, mean (SD)*	−17.0 (14.3)†	−18.1 (14.9)†	−31.4 (13.8)†	−33.8 (14.5)†
ΔDBP, mean (SD)*	−5.3 (8.7)†	−6.8 (7.7)†	−11.7 (8.0)†	−13.1 (9.4)†
BP <140/90, %‡	14.0	29.1	55.8	70.9

*Last observation carried forward. †P<.001 vs baseline. ‡Cumulative (percentage of the total number of patients in the efficacy cohort in each subpopulation). §P<.005 vs baseline. ||P<.01 vs baseline. ¶P<.05 vs baseline. HCTZ indicates hydrochlorothiazide; SBP, systolic blood pressure (BP); DBP, diastolic BP; Δ, change; ISH, isolated systolic hypertension; and BMI, body mass index.

and 49 of 169 subjects (29.0%) with OM 40 mg/d. Adding HCTZ enabled an additional 70 subjects to achieve BP goal: 45 subjects in the OM/HCTZ 40/12.5-mg/d treatment group and 25 patients in the OM/HCTZ 40/25-mg/d treatment group, with corresponding BP goal rates of 55.6% with HCTZ 12.5 mg/d and 70.4% with HCTZ 25 mg/d (Figure 2). BP normalization (<120/80 mm Hg) also showed a dose-dependent increase, with 1.2% of subjects achieving BP normalization with OM monotherapy, 5.9% with the addition of HCTZ 12.5 mg/d, and 15.4% with OM/HCTZ 40/25 mg/d (Table II).

Fifty-two subjects (30.8%) reached the SBP goal of <140 mm Hg with OM monotherapy; an additional 75 subjects reached goal with OM/HCTZ combination therapy, resulting in a cumulative total of 127 of 169 subjects (75.1%) reaching SBP goal. SBP normalization, defined as SBP <120 mm Hg, was achieved by 27 of 169 subjects (16.0%) by the end of the 12-week study.

Efficacy in Subpopulations of Subjects. The post hoc analysis of efficacy in subpopulations of subjects stratified by age, ISH, race, sex, and BMI showed that OM and OM/HCTZ were effective in lowering BP in all subpopulations (Table III; P<.05 vs baseline for all). BP goal attainment was dose dependent in all subpopulations. Because this study was not powered to detect differences in efficacy among subpopulations, such statistical comparisons were not conducted.

Safety

Drug-Related Clinical Adverse Events. OM monotherapy or in combination with HCTZ was well tolerated in subjects with stage 2 hypertension. The proportion of subjects with at least 1 drug-related, treatment-emergent clinical adverse event was similar in subjects exposed to OM 20 mg/d or 40 mg/d, and OM/HCTZ 40/12.5 mg/d or 40/25 mg/d (Table IV). The most frequently reported (≥2%) drug-related clinical adverse event was dizziness, followed by fatigue, with the highest frequencies for both occurring with combination therapy (Table IV). Symptomatic hypotension occurred in 1 OM/HCTZ 40/12.5-mg/d recipient. Most adverse events were mild or moderate in severity.

Drug-Related Laboratory Adverse Events. None of the subjects treated with OM 20 mg/d or 40 mg/d monotherapy or OM/HCTZ 40/12.5 mg/d combination therapy experienced a drug-related laboratory adverse event; however, 8 subjects (5.6%) receiving OM/HCTZ 40/25 mg/d experienced a laboratory change possibly related to the study drug (Table IV). The most frequently reported (≥2%) laboratory adverse events in this treatment group were elevated serum creatinine and elevated γ-glutamyltransferase; however, these elevations were considered not clinically significant.

Clinical Laboratory Evaluations. *Hematology*: A review of the mean and median values for red blood cell parameters, white blood cell count, differential white blood cell count, and platelets generally showed little change from baseline to the final visit regardless of dose (data not shown).

Serum Chemistry: The mean and median values for other laboratory findings showed little change from baseline to the final visit (Table V). Mean serum

Table IV. Drug-Related,* Treatment-Emergent Clinical Adverse Events and Laboratory Adverse Events Occurring in 2% or More of Subjects in Any Treatment Group (Safety Cohort)

Adverse Event, No. (%)†	OM 20 mg/d (N=170)	OM 40 mg/d (N=160)	OM/HCTZ 40/12.5 mg/d (N=157)	OM/HCTZ 40/25 mg/d (N=144)
Any clinical‡	7 (4.1)	6 (3.8)	10 (6.4)	9 (6.3)
Dizziness	1 (0.6)	1 (0.6)	6 (3.8)	7 (4.9)
Fatigue	0 (0)	0 (0)	1 (0.6)	3 (2.1)
Any laboratory	0 (0)	0 (0)	0 (0)	8 (5.6)
Serum creatinine >3.0 mg/dL	0 (0)	0 (0)	0 (0)	3 (2.1)
GGT >300 U/L	0 (0)	0 (0)	0 (0)	3 (2.1)

*Only events considered by the investigator as definitely, probably, or possibly related to study drug are included. †Adverse events listed are those that occurred at each titration step; numbers shown are not cumulative. ‡Clinical adverse events do not include laboratory adverse events. OM indicates olmesartan medoxomil; HCTZ, hydrochlorothiazide; and GGT, γ-glutamyltransferase.

potassium, glucose, and uric acid levels remained within normal limits during treatment with both OM/HCTZ combinations (Table VI). Mean glucose and uric acid levels increased with increasing doses of HCTZ but this trend was not clinically significant. Despite the slight elevation in uric acid levels in some subjects, none reported gout.

Serious Adverse Events. Only 4 subjects experienced a total of 8 treatment-emergent clinical adverse events that were considered serious but unrelated to the study drug; all of these subjects recovered without sequelae. These events were coronary artery disease, foot ulceration, dizziness, hemoptysis, pneumonia, hypotension, diabetic ulcer, and ankle fracture. The first 2 of these events occurred with OM monotherapy; the remaining 6 occurred with OM/HCTZ 40/12.5 mg/d. No clinically significant changes in ECG were observed.

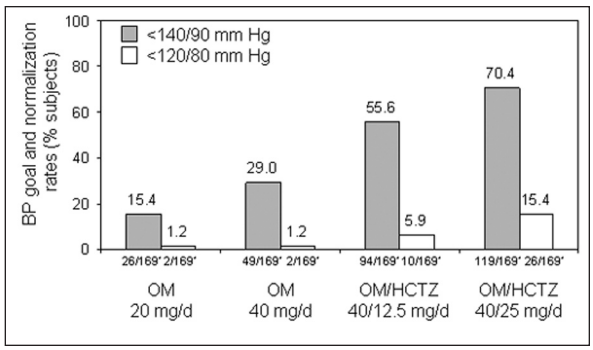

*Figure 2. Proportion of subjects who achieved blood pressure (BP) goal (<140/90 mm Hg) and BP normalization (<120/80 mm Hg). *Cumulative number of subjects who achieved BP goal or normalization out of the total 169 subjects in the efficacy cohort. OM indicates olmesartan medoxomil; HCTZ, hydrochlorothiazide.*

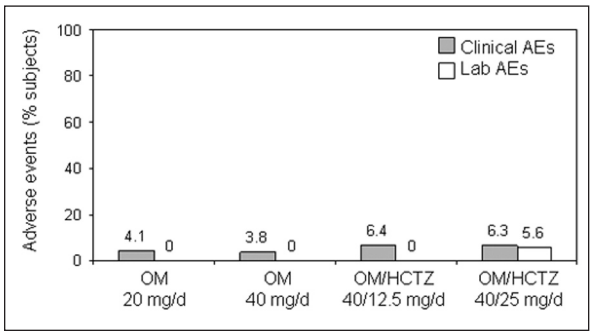

Figure 3. Percentage of subjects who experienced at least 1 clinical or laboratory adverse event (AE) at the end of each treatment period. OM indicates olmesartan medoxomil; HCTZ, hydrochlorothiazide.

DISCUSSION

This study confirms the antihypertensive efficacy of combining HCTZ with OM for the treatment of stage 2 systolic hypertension. Titration of OM and the addition of increasing doses of HCTZ produced significant dose-dependent mean reductions in SBP, enabling the majority of subjects to achieve recommended BP goals. In addition, approximately 15% of this population with stage 2 systolic hypertension achieved full BP normalization (<120/80 mm Hg). Data for hypertensive subpopulations (based on a post hoc analysis of subjects stratified by age, sex, race, and body weight) indicated that the response to combination therapy was similar in all subgroups. We acknowledge that the sample sizes in the subgroups are too small to provide sufficient statistical power to reach firm conclusions.

These results are consistent with findings from previous studies that showed greater reductions in BP when ARBs, ACEIs, or β-blockers were combined with HCTZ compared with either agent alone.[13–16,24] In individuals with mild-to-moderate essential hypertension, combining maximum doses of valsartan or irbesartan with HCTZ 25 mg/d reduced mean SBP by an additional 10.3 and 8.2 mm Hg, respectively, when compared with ARB monotherapy (P<.001 for either combination).[13,14] These greater BP reductions can be attributed

Table V. Clinical Laboratory Evaluation: Summary of Serum Chemistry Data From Baseline to End of Study (Safety Cohort)

Laboratory Test*	Baseline (N=170)	OM 20 mg/d (N=170)	OM 40 mg/d (n=160)	OM/HCTZ 40/12.5 mg/d (n=157)	OM/HCTZ 40/25 mg/d (n=144)
Total bilirubin, mg/dL	0.46	0.39	0.45	0.45	0.45
AKP, U/L	81.4	77.6	78.3	80.8	79.5
ALT, U/L	23.3	20.8	15.3	25.8	26.7
AST, U/L	22.8	25.8	18.5	24.1	25.0
GGT, U/L	31.4	31.1	25.5	36.7	37.4
Urea nitrogen, mg/dL	16.4	16.8	19.0	19.2	20.6
Creatinine, mg/dL	0.85	0.81	0.65	0.92	0.95
Calcium, mg/dL	9.48	9.53	9.63	9.61	9.68
Phosphorus, mg/dL	3.46	3.49	3.38	3.54	3.65
Total protein, g/dL	7.18	7.06	7.20	7.26	7.27
Albumin, g/dL	4.10	4.18	4.15	4.10	4.10
Sodium, mEq/L	141.4	140.6	139.8	140.2	140.3
Bicarbonate, mEq/L	25.67	25.41	24.20	27.07	27.66
Chloride, mEq/L	104.2	103.5	103.8	102.6	102.0
Cholesterol, mg/dL	200.0	201.7	235.3	201.5	200.6
LDL, mg/dL	123.8	116.3	135.0	121.5	118.3
HDL, mg/dL	48.4	60.3	60.3	49.6	49.6
Triglycerides, mg/dL	149.0	126.2	199.7	164.4	178.0

*Mean values. OM indicates olmesartan medoxomil; HCTZ, hydrochlorothiazide; AKP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; LDL, low-density lipoprotein cholesterol; and HDL, high-density lipoprotein cholesterol.

to the complementary mechanisms of action of HCTZ with agents that block the renin-angiotensin-aldosterone system (RAAS). HCTZ activates the RAAS, leading to enhanced responsiveness to angiotensin receptor blockade.[23,25] Conversely, blocking the RAAS converts hypertension to salt sensitivity, which is more responsive to diuretics.

Diuretics are particularly effective in the elderly,[26] who have the highest incidence of systolic hypertension,[27] primarily as a result of central arterial stiffening with age.[1,28] The results of the post hoc analysis from this study suggest that the OM/HCTZ treatment regimen was effective in subjects 65 years and older. In addition, this regimen was effective in individuals with ISH, allowing slightly more than two thirds (68.3%) to achieve SBP goal. Antihypertensive treatment regimens that effectively lower SBP and enable people to achieve recommended BP goals will become increasingly important as the US population ages.[29]

SBP is more difficult to control than DBP; in the Veterans Administration study,[30] approximately 70% of subjects achieved a DBP of <90 mm Hg, whereas only about 25% achieved an SBP of <140 mm Hg. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[4] 92% of subjects achieved a DBP of <90 mm Hg and 67% achieved an SBP of <140 mm Hg after 5 years of therapy, and, importantly, 63% of these individuals were taking 2 or more antihypertensive agents. Clinical trial data from the Multiple Risk Factor Intervention Trial (MRFIT)[31] and the Hypertension Optimal Treatment (HOT)[32] trial demonstrated that even with aggressive BP management, DBP control rates (>90%) were still much higher than SBP control rates (<60%). As a significant correlation exists between SBP elevations and the increased risk of heart failure, stroke, and kidney failure, adequate control of SBP has important clinical benefits, particularly in the aging population.[33–36] Importantly, treating to BP goal has been shown to reduce the risk of major cardiovascular events and mortality in people with systolic hypertension.[37,38]

The OM-based treatment with a diuretic regimen used in this study allowed the majority of subjects to achieve the recommended BP goal of <140/90 mm Hg. Adding low-dose HCTZ to the maximum dose of OM nearly doubled the proportion of subjects who achieved BP goal (from 29% to 56%). In addition, this approach enabled >15% of subjects to achieve the more stringent goal of BP normalization (<120/80 mm Hg). As expected, a substantial proportion of subjects required combination therapy to achieve BP normalization, consistent with other data and the recommendation to

Table VI. Effects of Olmesartan Medoxomil (OM) in Combination With Hydrochlorothiazide (HCTZ) on Metabolic Parameters (Safety Cohort) at the End of Each Treatment

Metabolic Variable, Mean ± SD (No.)	Baseline	OM/HCTZ, mg/d 40/12.5	40/25
Potassium, mEq/L	4.30±0.43 (166)	4.30±0.46 (152)	4.28±0.45 (138)
Glucose, mg/dL	103.9±24.56 (167)	107.9±30.57 (152)	109.0±30.12 (140)
Uric acid, mg/dL	6.03±1.31 (168)	6.95±1.61 (153)	7.38±1.79 (141)

initiate treatment with 2 antihypertensive agents in individuals with stage 2 hypertension.[7] Fixed-dose combinations may help improve patient compliance by simplifying the treatment regimen.

The incremental mean reductions in BP with increasing doses of OM and HCTZ were achieved without significant increases in adverse events (Figure 3). This may be explained in part by ARBs offsetting some of the potential adverse metabolic effects of HCTZ.[18,26,39] Importantly, mean serum potassium, glucose, and uric acid levels remained within normal limits with both OM/HCTZ combinations. There were small changes in glucose levels observed at both HCTZ doses, a low-ceiling effect that is apparently independent of angiotensin II type 1 receptor blockade; however, no subject experienced a drug-related adverse event of increased blood glucose while taking OM/HCTZ up to the maximum 40/25-mg/d dose. High-dose HCTZ has been shown to decrease serum potassium levels,[18,22] but serum potassium remained essentially unchanged, suggesting that angiotensin II type 1 receptor blockade may prevent potassium depletion.[40] Increased serum uric acid levels occurred with both doses of HCTZ, although fewer than 1% of subjects receiving the maximum OM/HCTZ 40/25-mg/d dose experienced hyperuricemia, and no gout attacks were reported.

OM monotherapy and OM/HCTZ combination therapy were safe and well tolerated at the doses studied. Drug-related adverse events occurred in fewer than 10% of subjects. No dose–response relationship was observed, with the exception of laboratory adverse events, which occurred in 6% of subjects after the HCTZ dose was doubled from 12.5 mg/d to 25 mg/d; however, this result was not clinically significant. No clinically significant changes in potassium or glucose levels were observed with the addition of HCTZ. The most common laboratory abnormalities were elevations in serum creatinine and γ-glutamyltransferase, which were mild or asymptomatic and occurred in approximately 2% of subjects.

This study was designed to mimic real-world clinical practice, and, accordingly, subjects were not blinded to treatment allocation and no placebo comparison was used. Conditions, however, were reasonably tightly controlled. The use of an automated BP-measuring device and the objective nature of the efficacy end points minimized the potential for patient and physician bias. The results of the present study are also qualitatively and quantitatively similar to those of other randomized, placebo-controlled trials.[16,18]

CONCLUSIONS

An OM-based stepwise treatment algorithm can effectively reduce SBP in stage 2 systolic hypertension, enabling 3 of 4 subjects to achieve the recommended SBP goal of <140 mm Hg and 1 of 6 subjects to achieve full SBP normalization of <120 mm Hg. OM alone and in combination with HCTZ was well tolerated throughout the dosing range.

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APPENDIX

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