Original Paper

Comparison of Increasing Doses of Olmesartan Medoxomil, Losartan Potassium, and Valsartan in Patients With Essential Hypertension

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This 12-week, randomized, double-blind, forced-titration study compared the efficacy of 3 angiotensin receptor blockers. Patients received olmesartan medoxomil 20 mg, losartan potassium 50 mg, valsartan 80 mg, or placebo once daily. At week 4, doses were titrated to 40, 100, and 160 mg once daily for olmesartan, losartan, and valsartan, respectively. At week 8, losartan was increased to 50 mg twice daily and valsartan increased to 320 mg once daily (olmesartan remained at 40 mg once daily). The primary end point was mean change from baseline in seated diastolic blood pressure (SeDBP) at week 8. All 3 medications significantly reduced mean SeDBP from baseline compared with placebo at weeks 4, 8, and 12 (P<.001). At week 8, olmesartan reduced mean SeDBP more than losartan (P<.001); more patients in the olmesartan medoxomil group achieved a blood pressure goal of <140/90 mm Hg (P<.001). Olmesartan did not reduce mean SeDBP significantly compared with valsartan, although more patients attained blood pressure goal with olmesartan (P=.031). At week 12, all agents lowered blood pressure equivalently. (J Clin Hypertens. 2007;9:187–195) ©2007 Le Jacq

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Epidemiologic data have shown a direct and continuous relationship between elevated blood pressure (BP) and cardiovascular risk, independent of other risk factors.[1–5] These increases in cardiovascular risk occur with increases in BP over a range starting at 115/75 mm Hg.[4] This observation supports the concept that more aggressive BP control is important in the treatment of hypertension. For patients who require a BP-lowering intervention, drugs that inhibit the renin–angiotensin system, such as angiotensin receptor blockers (ARBs) (usually in combination with a diuretic) not only lower BP effectively but may also reduce target organ damage by mechanisms independent of BP reduction.[6]

In a previous 8-week study, the ARBs olmesartan medoxomil, losartan potassium, valsartan, and irbesartan were compared in recommended starting doses in the United States at the time of the study.[7] In that study, olmesartan medoxomil reduced diastolic BP (DBP) more than the other medications. Reductions in mean systolic BP (SBP) were not significantly different. Secondary (post hoc) analyses of these data demonstrated that a significantly higher percentage of patients achieved both cuff and 24-hour BP goals when treated with olmesartan medoxomil compared with losartan potassium and valsartan.[8,9] There was no difference in achieved BP goals with olmesartan medoxomil compared with irbesartan.[8,9]

The current study compared the efficacy of olmesartan medoxomil, losartan potassium, and valsartan across the range of recommended doses and dosing regimens in reducing BP and achieving BP goal in patients with essential hypertension over a 12-week period.

MATERIALS AND METHODS

Study Design

In this 12-week, randomized, double-blind, placebo-controlled, multicenter (109), forced-titration trial, a 4-week single-blind placebo run-in period was followed by randomization to 1 of 4 treatment groups in a 2:2:2:1 ratio: olmesartan medoxomil 20 mg, losartan potassium 50 mg, valsartan 80 mg, or placebo, all once daily. Doses were titrated to 40, 100, and 160 mg once daily for olmesartan medoxomil, losartan potassium, and valsartan, respectively, after 4 weeks of treatment. At week 8, doses were titrated to 50 mg twice daily for losartan potassium and 320 mg once daily for valsartan; the olmesartan medoxomil dose remained at the maximum recommended dose of 40 mg once daily. Patients were instructed to take their study medication in the morning at breakfast except for losartan potassium, which was to be taken both in the morning and the evening during weeks 9 through 12.

The study protocol and consent forms were reviewed and approved by an institutional review board at each of the 109 centers before initiation of the study. Each study participant gave written informed consent at the screening visit. The study was conducted in accordance with the institutional review board committee, informed consent regulations, and Declaration of Helsinki principles.

Patients

The study included men and women 18 years and older with primary hypertension. Inclusion in the study required a mean seated cuff DBP (SeDBP) between 100 and 115 mm Hg at placebo run-in at weeks 3 and 4, with a difference of no more than 10 mm Hg in the mean SeDBP between visits. Twelve-hour ambulatory BP monitoring was conducted at week 4 of the placebo run-in to establish a mean daytime DBP between 90 and 115 mm Hg.

Patients were excluded if they had serious medical disorders that might limit the evaluation of the efficacy or safety of active therapy or if they had a history of myocardial infarction, coronary angioplasty, bypass surgery, heart failure, cerebrovascular accident, or transient ischemic attack within the previous 6 months. Additional exclusion criteria were secondary hypertension; excluded medications including cardiovascular agents, central nervous system agents, and chronic use of adrenergic agents; clinically significant abnormal blood chemistry, hemoglobin, or urinalysis; drug abuse within 2 years, or a history of allergy to ARBs. Women who were pregnant, planning to become pregnant, or were breast-feeding were also excluded. Patients were withdrawn from the study if mean SeDBP exceeded 115 mm Hg or SeSBP exceeded 180 mm Hg or if adverse events (AEs) occurred that could not be tolerated.

Efficacy and Tolerability Assessments

Seated cuff BP was determined in triplicate, with 1 minute between measurements, after the patient had been sitting in the examination room for 5 minutes during clinic visits at weeks 1 to 4 of the placebo run-in period, and at weeks 2, 4, 6, 8, 10, and 12 of the double-blind active treatment period. During the active treatment period, measurements were obtained before 10 AM on the day of the study visit and within 21 to 27 hours of the previous morning dose of study medication. Patients were evaluated for safety throughout the placebo run-in and active treatment periods. Compliance and concomitant medications were also assessed at each visit.

End Points

The primary end point was the mean change from baseline in cuff SeDBP (measured 21–27 hours postdose) at week 8. Change in DBP was chosen as the primary end point because at the time this study was initiated, US Food and Drug Administration (FDA) guidelines (*Proposed Guidelines for the Clinical Evaluation of Antihypertensive Drugs, Draft 5/09/88*. Rockville, MD: Division of Cardio-Renal Drug Products) emphasized that the primary efficacy measure of an antihypertensive agent was the level of DBP reduction.

Secondary end points included the mean change in cuff SeSBP at weeks 2, 4, 6, 8, 10, and 12 and in office SeDBP at weeks 2, 4, 6, 10, and 12. An additional secondary efficacy end point was seated cuff combined BP goal rate, defined as the proportion of patients achieving SBP less than 140 mm Hg and DBP less than 90 mm Hg at weeks 4, 8, and 12. A secondary (post hoc) analysis was conducted to determine the proportion of patients achieving SBP/DBP less than 130/85 mm Hg at weeks 4, 8, and 12 (the recommended goal for patients with diabetes and chronic kidney disease at the time this study was conducted).[10] Week 12 of the study was analyzed to determine whether higher doses of the

Table I. Patient Demographics and Baseline Characteristics for the Intent-to-Treat Cohort*

	Olmesartan Medoxomil (n=199)	Losartan Potassium (n=200)	Valsartan (n=197)	Placebo (n=100)
Mean age, y (SD)	52.2 (9.6)	51.3 (10.5)	52.2 (10.3)	52.4 (10.0)
Patients ≤65 y, %	92.0	92.5	88.8	89.0
Race, %				
White	63.3	62.5	65.0	65.0
Black	22.1	23.5	18.8	22.0
Asian	1.5	2.5	1.5	2.0
Hispanic	13.1	10.5	14.2	11.0
Other	0	1.0	0.5	0
Men, %	62.8	60.5	66.0	52.0
Mean baseline SeSBP, mm Hg (SD)	155.4 (11.2)	155.0 (11.5)	154.3 (10.6)	153.9 (11.0)
Mean baseline SeDBP, mm Hg (SD)	103.5 (3.1)	103.6 (2.8)	103.3 (3.2)	103.2 (2.8)
Mean duration of HTN, y (SD)	8.5 (8.3)	8.9 (8.7)	10.4 (9.7)	9.0 (8.4)
Family history of HTN, %	71.9	65.5	65.5	70.0
Antihypertensive use in past 90 days, %	82.9	78.0	80.2	83.0
NSAID use, No. (%)†				
Indomethacin	0	1 (0.5)	0	5 (4.7)
Celecoxib	4 (1.9)	10 (4.8)	4 (2.0)	3 (2.8)
Rofecoxib	6 (2.9)	8 (3.9)	5 (2.5)	1 (0.9)
Ibuprofen	32 (15.5)	38 (18.4)	31 (15.3)	20 (18.9)
Naproxen	6 (2.9)	8 (3.9)	3 (1.5)	0
Acetylsalicylic acid	13 (6.3)	14 (6.8)	8 (3.9)	7 (6.6)

*There were no significant differences among treatment groups. †Nonsteroidal anti-inflammatory drug (NSAID) use values are for the randomized patient population: olmesartan medoxomil, n=207; losartan potassium, n=207; valsartan, n=203; placebo, n=106. SeSBP indicates seated cuff systolic blood pressure; SeDBP, seated cuff diastolic blood pressure; and HTN, hypertension.

ARBs (other than olmesartan medoxomil) demonstrated equivalence of BP reduction.

Statistical Analyses

The primary null hypothesis was that the treatment effect of olmesartan medoxomil 40 mg once daily is worse than that of losartan potassium 100 mg once daily or valsartan 160 mg once daily.

The secondary null hypotheses was that the treatment effect of olmesartan medoxomil 20 mg once daily is worse than that of losartan potassium 50 mg once daily or valsartan 80 mg once daily.

The tertiary null hypotheses was that the treatment effect difference in SeDBP of olmesartan medoxomil 40 mg once daily and losartan potassium 50 mg twice daily or valsartan 320 mg once daily is outside the equivalence limit of 3.5 mm Hg.

Based on practical considerations, a total sample size of 700 patients (200 patients per active treatment arm and 100 for the placebo arm) was chosen. Based on published data on the treatment effects of each agent, it was estimated that using a 1-sided significance level of .05 with Dunnett's adjustment, 200 patients per active treatment arm would provide approximately 60% power.

The intent-to-treat population was defined as patients who received at least 1 dose of study drug and had a baseline BP measurement and at least 1 postbaseline BP assessment. The safety population comprised all randomized patients who received at least 1 dose of study drug.

For the analyses of BP reductions, missing BP values were imputed using the last-observation-carried-forward method by which a patient's last visit assessment data are carried forward for analysis at each subsequent time point within that dose level (ie, when the week 4, 8, or 12 value was missing, the week 2, 6, 10, or early termination value at the same dose level was substituted for the missing observation, respectively). No differences in statistical significance were noted for any drug treatment at any time point for BP decreases with or without the last observation carried forward.

Analysis of covariance (ANCOVA) was used to analyze numeric mean reductions in BP from baseline, with baseline as the covariate and center and treatment as factors, where the center was a random effect. A 1-sided Dunnett test was used to compare olmesartan medoxomil with losartan potassium and valsartan to ensure that the overall type I error

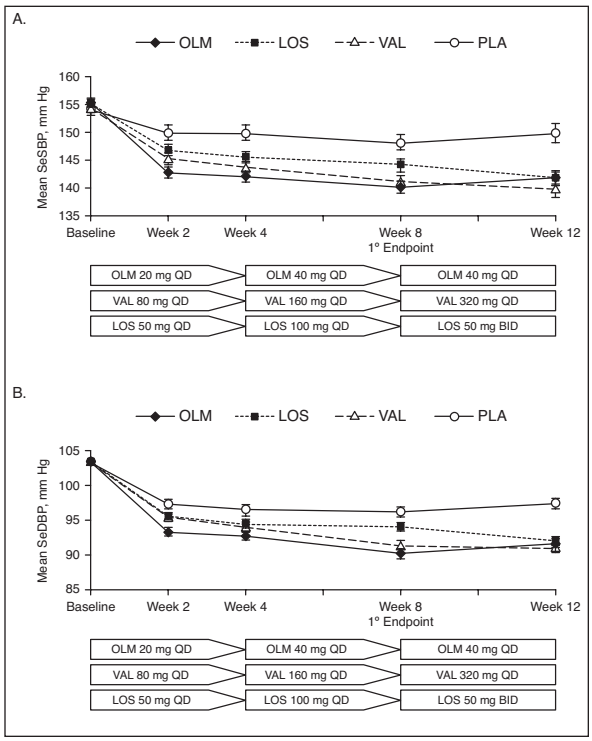

Figure 1. Time course of mean (A) seated cuff systolic blood pressure (SeSBP) and (B) seated cuff diastolic blood pressure (SeDBP) values in response to olmesartan medoxomil (OLM), losartan potassium (LOS), valsartan (VAL), and placebo (PLA) from baseline to week 12 (last observation carried forward within each dose level: when the week 8 value was missing, the week 6 or early termination value at the same dose level was substituted for the missing observation). Error bars represent SEM.

did not exceed 5% for multiple comparisons. The least squares means for treatment effect difference among medications were estimated and the SE of the estimated difference was used to construct the 90% confidence intervals (CIs) for the treatment effect differences. An analysis of BP goal rates was conducted at weeks 4, 8, and 12 using a chi-square method to test the hypothesis that there was no difference in rates among drugs, and 95% CIs were calculated. To validate the study, the change from study baseline in cuff DBP and SBP at weeks 2, 4, 6, 8, and 12 were compared between placebo and each active treatment for each treatment dose/regimen by the same ANCOVA model using a 2-sided test at 5% level without multiplicity adjustment.

A subsequent reanalysis of efficacy data from this trial was performed because of the necessary disqualification of 11 patients from a single study site. The revised data do not alter findings formerly reported for the predetermined trial end points or secondary analyses, nor for the overall conclusions of the study.[11–14] The intent-to-treat analysis, therefore, includes data from only 108 centers. Data reported for patient disposition and AEs include all 109 centers.

RESULTS

Patient Characteristics and Demographics

Of 723 patients randomized, 696 were included in the intent-to-treat analysis. Patient characteristics and demographics are shown in Table I. There were no significant differences in patient characteristics or demographics among the 4 arms of the study.

Efficacy

BP Reduction From Baseline. All 3 ARBs significantly reduced mean SeDBP and SeSBP from baseline compared with placebo at weeks 2, 4, 6, 8, 10, and 12 ($P<.05$ for SeDBP, and $P<.05$ for SeSBP) (Figure 1 and Table II).

The use of olmesartan medoxomil resulted in greater mean reductions in SeSBP and SeDBP early in the study compared with the comparator ARBs (ie, at weeks 2 and 4) (Figure 2). After 2 weeks of treatment, patients receiving this medication (20 mg once daily) had significantly greater reductions in mean SeDBP and SeSBP than did those receiving losartan potassium 50 mg once daily ($P=.005$ for SeDBP; 90% CI, –3.33 to –0.63; $P<.001$ for SeSBP, 90% CI, –6.59 to –2.26) or valsartan 80 mg once daily ($P=.001$ for SeDBP; 90% CI, –3.69 to –0.97; $P=.002$ for SeSBP; 90% CI, –5.75 to –1.40) (Table II). After 4 weeks of treatment, patients receiving olmesartan medoxomil 20 mg once daily also had significantly greater reductions in mean SeDBP and SeSBP than did those receiving losartan potassium 50 mg once daily ($P=.037$ for SeDBP; 90% CI, –2.95 to –0.10; $P<.001$ for SeSBP; 90% CI, –6.16 to –1.72) or valsartan 80 mg once daily ($P=.049$ for SeDBP; 90% CI, –2.87 to –0.01; $P=.012$ for SeSBP, 90% CI,–5.14 to –0.68) (Table II).

After 8 weeks of treatment, patients receiving olmesartan medoxomil 40 mg once daily had significantly greater reductions in mean SeDBP and SeSBP than did those receiving losartan potassium 100 mg once daily ($P<.001$ for both; SeDBP 90% CI, –5.00 to –1.99; SeSBP 90% CI, –6.66 to –1.88) (Table II, Figure 3A, and Figure 3B), but no significant difference compared with the valsartan treatment group ($P=.104$ for SeDBP; 90% CI, –2.74 to 0.29; $P=.081$ for SeSBP; 90% CI, –4.60 to 0.21).

After 12 weeks of treatment with the maximum-approved dosages of the 3 ARBs tested, reductions in mean SeDBP and SeSBP (Table II) were equivalent.

Combined SBP/DBP Goal Rates. A significantly greater percentage of patients achieved the

Table II. Least Squares Mean SeSBP and SeDBP Reductions at Weeks 2, 4, 8, and 12 (Last Observation Carried Forward for Weeks 4, 8, and 12) and BP Goal Rates at Weeks 4, 8, and 12

	Olmesartan Medoxomil	Losartan Potassium	Valsartan	Placebo
Week 2	(n=199)	(n=200)	(n=197)	(n=100)
BP changes, mm Hg (90% CI)				
ΔSeSBP	–12.9 (–14.2 to –11.5)*†‡	–8.5 (–9.8 to –7.1)*	–9.3 (–10.7 to –8.0)*	–4.5 (–6.3 to –2.6)
ΔSeDBP	–10.2 (–11.1 to –9.3)* ‡§	–8.2 (–9.1 to –7.3)*	–7.9 (–8.8 to –7.0)*	–5.9 (–7.2 to –4.7)
BP goals, % achieving				
<140/90 mm Hg	22.1*	17.5*	14.7*	7.0
<130/85 mm Hg	7.0*§	2.5	3.0	0.0
BP goals, % not achieving				
SBP ≥140 or DBP ≥90 mm Hg	77.9	82.5	85.3	93.0
SBP ≥130 or DBP ≥85 mm Hg	93.0	97.5	97.0	100.0
Week 4				
BP changes, mm Hg (90% CI)	(n=199)‖	(n=200)‖	(n=197)‖	(n=100)‖
ΔSeSBP	–13.5 (–14.9 to –12.1)*†‡	–9.6 (–11.0 to –8.2)*	–10.6 (–12.0 to –9.2)*	–4.2 (–6.1 to –2.3)
ΔSeDBP	–10.6 (–11.7 to –9.6)* ‡§	–9.1 (–10.2 to –8.1)*	–9.2 (–10.2 to –8.2)*	–6.7 (–8.0 to –5.4)
BP goals, % achieving	(n=190)¶	(n=194)¶	(n=191)¶	(n=97)¶
<140/90 mm Hg	27.4*	20.6*	22.0*	10.3
<130/85 mm Hg	11.6‡*	6.2	5.2	4.1
BP goals, % not achieving				
SBP ≥140 or DBP ≥90 mm Hg	72.6	79.4	78.0	89.7
SBP ≥130 or DBP ≥85 mm Hg	88.4	93.8	94.8	95.9
Week 8				
BP changes, mm Hg (90% CI)	(n=189)‖	(n=192)‖	(n=189)‖	(n=94)‖
ΔSeSBP	–15.2 (–16.7 to –13.7)*†	–10.9 (–12.4 to –9.4)*	–13.0 (–14.5 to –11.4)*	–6.1 (–8.2 to –4.0)
ΔSeDBP	–12.9 (–13.9 to –11.8)*†	–9.4 (–10.4 to –8.3)*	–11.6 (–12.7 to –10.6)*	–6.9 (–8.3 to –5.5)
BP goals, % achieving	(n=184)¶	(n=187)¶	(n=183)¶	(n=89)¶
<140/90 mm Hg	39.7*†‡	19.8	29.0*	12.4
<130/85 mm Hg	14.7*§	7.0*	13.1*	1.1
BP goals, % not achieving				
SBP ≥140 or DBP ≥90 mm Hg	60.3	80.2	71.0	87.6
SBP ≥130 or DBP ≥85 mm Hg	85.3	93.0	86.9	98.9
Week 12				
BP changes, mm Hg (90% CI)	(n=182)‖	(n=180)‖	(n=181)‖	(n=87)‖
ΔSeSBP	–13.9 (–15.6 to –12.1)*	–13.4 (–15.2 to –11.7)*	–14.8 (–16.5 to –13.1)*	–4.4 (–6.8 to –2.0)
ΔSeDBP	–11.7 (–12.8 to –10.5)*	–11.5 (–12.7 to –10.4)*	–12.4 (–13.5 to –11.3)*	–5.7 (–7.2 to –4.2)
BP goals, % achieving	(n=170)¶	(n=177)¶	(n=180)¶	(n=86)¶
<140/90 mm Hg	35.3*	33.3*	30.6*	10.5
<130/85 mm Hg	18.2*	11.3*	11.1*	2.3
BP goals, % not achieving				
SBP ≥140 or DBP ≥90 mm Hg	64.7	66.7	69.4	89.5
SBP ≥130 or DBP ≥85 mm Hg	81.8	88.7	88.9	97.7

BP indicates blood pressure; CI, confidence interval; SeSBP, seated cuff systolic BP (SBP); and SeDBP, seated cuff diastolic BP (DBP). *P<.05 vs placebo. †P<.001 vs losartan potassium. ‡P<.05 vs valsartan. §P<.05 vs losartan potassium. ‖The number of patients in the intent-to-treat efficacy cohort, using last observation carried forward for weeks 4, 8, and 12 (when the week 4, 8, or 12 value was missing, the week 2, 6, 10, or early termination value at the same dose level was substituted for the missing observation, respectively). ¶The number of patients with available observations at the visit.

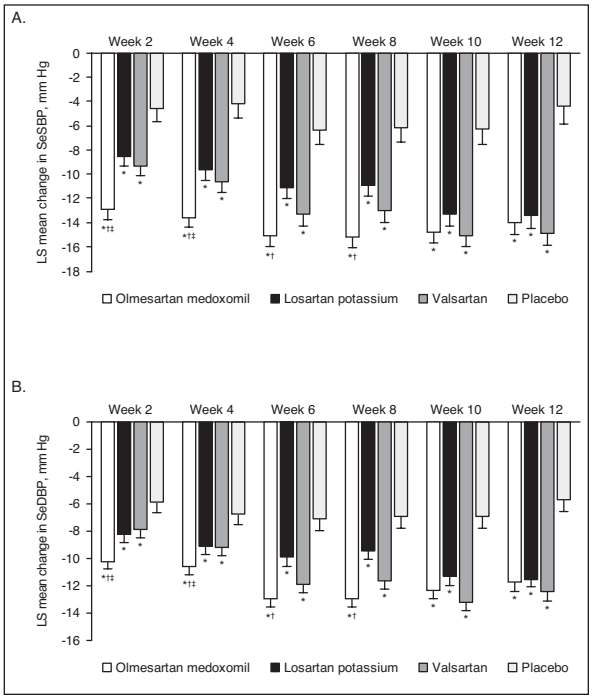

*Figure 2. Time course of change from baseline in least squares (LS) mean (A) seated cuff systolic blood pressure (SeSBP) and (B) seated cuff diastolic blood pressure (SeDBP) values in response to olmesartan medoxomil, losartan potassium, valsartan, and placebo at each assessment from week 2 through week 12. Error bars represent SEM. *P<.05 vs placebo; †P<.05 vs losartan potassium; ‡P<.05 vs valsartan. Statistical comparisons between losartan potassium and valsartan were not performed.*

recommended SBP/DBP goal of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) of less than 140/90 mm Hg with olmesartan medoxomil compared with losartan potassium (39.7% vs 19.8%, respectively; *P*<.001; 95% CI, 10.8–29.0) (Figure 3C), and with olmesartan medoxomil compared with valsartan (39.7% vs 29.0%, respectively; *P*=.031; 95% CI, 1.1–20.4) after 8 weeks of treatment.

The percentage of patients achieving a BP goal less than 140/90 mm Hg at weeks 2, 4, and 12 was not significantly different among the 3 medications (Table II).

The percentage of patients achieving BP less than 130/85 mm Hg was determined; this was the goal for patients with diabetes or chronic kidney disease recommended by JNC VI, which was current at the time this study was conducted.[10] At week 2, the percentage of patients achieving BP less than 130/85 mm Hg was not significantly different for olmesartan medoxomil compared with valsartan (7.0% vs 3.0%, respectively; *P*=.070; 95% CI, –0.3 to 8.3), but a significantly larger percentage of patients achieved this BP goal with olmesartan medoxomil compared with losartan potassium (7.0% vs 2.5%, respectively; *P*=.033; 95% CI, 0.4–8.7). But at week 4 there was no significant difference between the 2 drugs.(11.6% vs 6.2%, respectively; *P*=.063; 95% CI, –0.3 to 11.1). There was, however, a difference between olmesartan medoxomil and valsartan (11.6% vs 5.2%, respectively; *P*=.026; 95% CI, 0.8–11.9) (Table II).

At week 8, a significantly larger proportion of patients achieved BP less than 130/85 mm Hg with olmesartan medoxomil compared with losartan potassium (14.7% vs 7.0%, respectively; *P*=.016; 95% CI, 1.4–14.0) (Table II), but was not greater than with valsartan (14.7% vs 13.1%, respectively; *P*=.666; 95% CI, –5.5 to 8.6).

With the highest approved doses and dosing regimens, the percentage of patients achieving BP less than 130/85 mm Hg was similar with the 3 ARBs tested (Table II).

Tolerability

Total discontinuations during the study were 35 of 207 patients (16.9%), 28 of 207 (13.5%), 21 of 203 (10.3%), and 19 of 106 (17.9%) in the olmesartan medoxomil, losartan potassium, valsartan, and placebo safety cohort groups, respectively. Overall, the most common reasons for discontinuation were patient request, uncontrolled BP, and AEs.

Most AEs were of mild-to-moderate severity. Headache was the most commonly reported AE, occurring in 82 of 723 (11.3%) of all randomized patients (Table III). The incidence of drug-related AEs was similar among the treatment groups. Seven of 723 randomized patients (<1%) reported serious AEs that met the definition of treatment-emergent, but none was deemed related to a study drug, and 1 patient died during the placebo run-in period of the study.

No hypotensive events were reported in this study; however, dizziness, which may have been a symptom of hypotension, was reported in 5.8%, 4.8%, 3.9%, and 3.8% of patients receiving olmesartan medoxomil, losartan potassium, valsartan, and placebo, respectively. Two patients (1 on olmesartan medoxomil 20 mg and 1 on olmesartan medoxomil 40 mg) discontinued due to dizziness; the former was thought to be possibly related and the latter unrelated to the study drug.

DISCUSSION

The current study assessed the efficacy of olmesartan medoxomil at the maximum recommended dose

Table III. Overall Incidence of Adverse Events (AEs) to Week 12 in the Safety Population

AEs, No. (%)	Olmesartan Medoxomil (n=207)	Losartan Potassium (n=207)	Valsartan (n=203)	Placebo (n=106)
Incidence				
≥1	107 (51.7)	103 (49.8)	110 (54.2)	57 (53.8)
≥1 drug-related	30 (14.5)	32 (15.5)	30 (14.8)	16 (15.1)
≥1 severe	5 (2.4)	7 (3.4)	7 (3.4)	4 (3.8)
≥1 serious treatment-emergent	5 (2.4)	0	2 (1.0)	1 (0.9)
Discontinued due to AEs	9 (4.3)	4 (1.9)	5 (2.5)	2 (1.9)
Treatment-emergent AEs in >3% of patients in any treatment group				
Back pain	2 (1.0)	8 (3.9)	7 (3.4)	2 (1.9)
Fatigue	7 (3.4)	10 (4.8)	6 (3.0)	4 (3.8)
Dizziness	12 (5.8)	10 (4.8)	8 (3.9)	4 (3.8)
Headache	24 (11.6)	23 (11.1)	16 (7.9)	19 (17.9)
Diarrhea	6 (2.9)	4 (1.9)	12 (5.9)	5 (4.7)
Nausea	9 (4.3)	3 (1.4)	3 (1.5)	2 (1.9)
Sinusitis	8 (3.9)	7 (3.4)	8 (3.9)	3 (2.8)
Upper RTI	17 (8.2)	17 (8.2)	25 (12.3)	11 (10.4)

There were no significant differences among treatment groups. RTI indicates respiratory tract infection.

of 40 mg once daily compared with 100 mg once daily of losartan potassium and 160 mg once daily of valsartan after 8 weeks of therapy (primary end point). In addition, because the comparators in this study each had a third dosing regimen (ie, a 50-mg twice-daily regimen for losartan potassium and 320 mg of valsartan once daily), equivalence to the olmesartan medoxomil 40-mg once-daily dose was chosen as the end-of-study end point (week 12). Losartan potassium prescribing information indicates that this agent may be administered either once or twice daily, whereas valsartan prescribing information indicates only once-daily administration for the treatment of hypertension. Therefore, only losartan potassium was administered as a twice-daily regimen during weeks 9 to 12. The dosing regimens used in this study reflect those used in common therapeutic practice.

A clear dose effect of all of the ARBs examined in this study was observed for mean SBP and DBP lowering. The use of olmesartan medoxomil resulted in greater decreases early in the trial (at weeks 2 and 4), however, suggesting an earlier onset of antihypertensive effect with olmesartan medoxomil. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial[15,16] demonstrated the importance of early BP lowering for reducing the incidence of cardiovascular events.

At week 8, significantly greater mean reductions in BP and higher rates of goal attainment were observed for olmesartan medoxomil compared with losartan potassium. Although the differences in BP between olmesartan medoxomil and valsartan did not reach statistical significance, more patients reached the BP goal of less than 140/90 mm Hg with olmesartan medoxomil 40 mg (maximum dose) than with valsartan 160 mg (1 of 2 starting doses) (39.7% vs 29.0%, respectively; $P<.05$).

The 12-week time point was designed to determine equivalence of the highest-approved doses and dosing regimens of these ARBs. At week 12, equivalent BP lowering was observed among olmesartan medoxomil, losartan potassium, and valsartan.

Approximately one third of patients enrolled in this study were able to achieve a BP goal of less than 140/90 mm Hg with ARB monotherapy, but the remaining two thirds did not achieve this BP goal with the maximum-approved doses and dosing regimens of the ARBs tested. This suggests the need for multiple drug therapy to achieve BP reduction in a majority of patients who are initially treated with an ARB.

In recent years, the emphasis of antihypertensive treatment has shifted from reductions in mean SeDBP and SeSBP to the control of BP at goal levels or below to limit the progression of serious cardiovascular disease.[17–19] For example, JNC 7 set a goal of less than 140/90 mm Hg for most patients and less than 130/80 mm Hg for those with diabetes mellitus or chronic kidney disease.[18] The most recent Joint British Societies' guidelines set a slightly more stringent BP goal of less than 140/85 mm Hg as the optimal goal for patients without cardiovascular disease, diabetes, or chronic renal disease.[19]

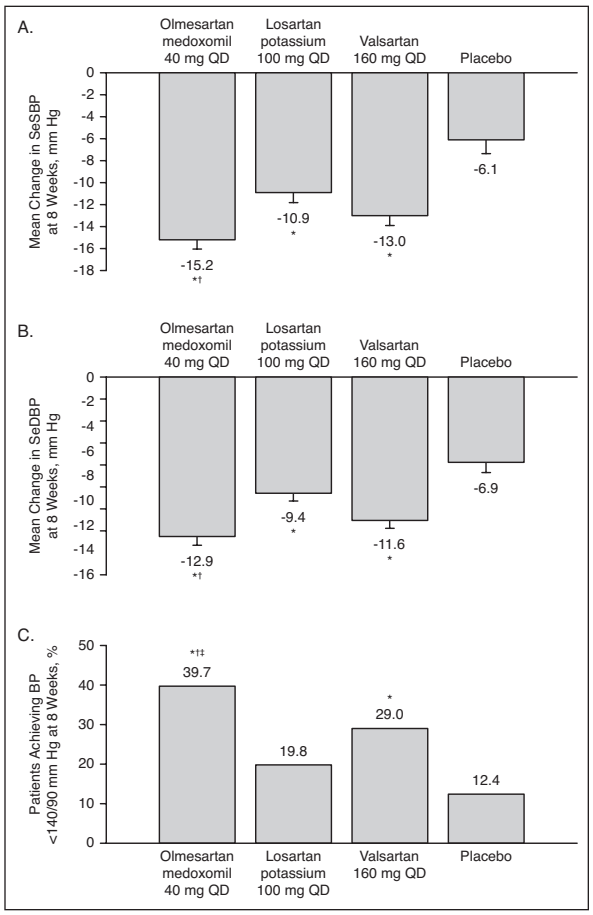

*Figure 3. (A) Mean reductions in seated cuff systolic blood pressure (SeSBP) from baseline to week 8 (least squares means, last observation carried forward (LOCF) within each dose level: when the week 8 value was missing, the week 6 or early termination value at the same dose level was substituted for the missing observation). *P<.05 vs placebo; †P<.001 vs losartan potassium. Error bars represent SEM. (B) Mean reductions in seated cuff diastolic blood pressure (SeDBP) from baseline to week 8 (least squares means, LOCF within each dose level: when the week 8 value was missing, the week 6 or early termination value at the same dose level was substituted for the missing observation). *P<.05 vs placebo; †P<.001 vs losartan potassium. Error bars represent SEM. (C) Percentage of patients achieving a blood pressure (BP) goal of less than 140/90 mm Hg after 8 weeks of treatment. *P<.05 vs placebo; †P<.001 vs losartan potassium; ‡P<.05 vs valsartan. Statistical comparisons between losartan potassium and placebo and valsartan and placebo were not performed.*

Despite the recognized cardiovascular benefits of achieving BP reduction to less than 140/90 mm Hg, some studies continue to report responder rates rather than the percentage of patients achieving recommended SBP/DBP goals.[20] Responder rates report the proportion of patients responding to a particular therapy, typically assessed by the percentage of patients attaining a predetermined, arbitrary level of BP change (usually ≥10 mm Hg reduction from baseline in DBP), as well as the percentage of patients achieving a set DBP target (usually DBP ≤90 mm Hg). Consequently, a patient may be counted as a responder despite not having BP controlled to less than 140/90 mm Hg. The current study provides clinically relevant efficacy information on the ability of several ARBs to achieve recommended BP goals when up-titrated to maximum approved monotherapy doses.

Limitations of the Study

In this study, olmesartan medoxomil was compared with 2 other ARBs, losartan potassium and valsartan. One potential limitation is that at the time this study was initiated, the starting dose for valsartan was 80 mg; since that time, valsartan 160 mg has also become a recommended starting dose. The dose escalation scheme is similar to that used in clinical practice, however, because valsartan 80 mg once daily can still be administered as an initial starting dose. Another limitation of this study is that the 12-week treatment interval was not a long enough period to assess long-term BP-lowering efficacy for the evaluated agents. Consequently, a trial of longer duration would be needed to determine the long-term BP-lowering efficacy for each agent and to subsequently make long-term efficacy comparisons among the agents. Finally, the study was designed to determine the difference in BP at trough only, and did not assess BP at other time points. Twenty-four–hour ambulatory BP monitoring would need to be performed in a future study to compare BP reductions throughout the dosing interval.

CONCLUSIONS

At maximum titrated doses, the BP-lowering capabilities of these commonly used ARBs are similar after a 3-month treatment period. Some early differences in achieving goal BPs were noted with olmesartan medoxomil, and these differences were significant at 8 weeks compared with losartan potassium and valsartan.

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