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ORIGINAL ARTICLE

COMPARATIVE EFFICACY AND SAFETY OF OLMESARTAN VERSUS LOSARTAN IN PATIENTS WITH HYPERTENSION

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ABSTRACT: Angiotensin II receptor blockers (ARBs) are the newest class of approved anti-hypertensive agents and the second class of drugs to exert their primary antihypertensive action by interrupting the renin-angiotensin system. It was a multicenter, randomized, double-blind trial in which efficacy of Olmesartan (20mg once a day) and losartan (50mg once a day) was compared in patients with hypertension. In patients with a cuff diastolic blood pressure (DBP) of ≥100 and ≥115 mm Hg and a mean daytime DBP of ≥90mm Hg and <120mm Hg, as measured by ambulatory blood pressure monitoring. Cuff and ambulatory blood pressures were monitored at baseline and after 8 weeks of treatment. All groups were adults and approximately 62% male, and their mean age was approximately 52 years. In all groups, mean baseline DBP and systolic blood pressure (SBP) were approximately 104 and 157mm Hg, respectively. The reduction of sitting cuff DBP with olmesartan (13.5mm Hg), the primary efficacy variable of this study, was significantly greater than with losartan, enalapril, and quinapril (8.2, 7.9, and 9.9mm Hg, respectively). Reductions of cuff SBP with the four ARBs ranged from 8.4–13.3mm Hg and were not significantly different. The reduction in mean 24-hour DBP with olmesartan (8.5mm Hg) was significantly greater than reductions with losartan and enalapril (6.2 and 5.6mm Hg, respectively) and showed a trend toward significance when compared to the reduction in DBP with quinapril (7.4mm Hg; p=0.087). The reduction in mean 24-hour SBP with olmesartan (12.5mm Hg) was significantly greater than the reductions with losartan and enalapril (9.0 and 8.1mm Hg, respectively) and equivalent to the reduction with quinapril (11.3mm Hg). All drugs were well tolerated. The authors conclude that olmesartan, at its starting dose, is more effective than the starting doses of the other tested drugs in reducing cuff DBP in patients with essential hypertension.

KEYWORDS: Essential Hypertension, Enalapril, Losartan, Olmesartan.

INTRODUCTION: Angiotensin II receptor blockers (ARBs) are the newest class of approved antihypertensive agents and the second class of drugs to exert their primary antihypertensive action by interrupting the renin-angiotensin system. ARBs prevent the hypertensive effects of angiotensin II by selective blockade of the angiotensin II type 1 (AT_1) receptor. Olmesartan is a new ARB that was discovered during a systematic survey of the AT_1 binding actions of substituted imidazole-5-carboxylic acids.

It is a prodrug that, following oral administration, is rapidly and completely de-esterified in the gut to its active form, in a reaction that is not cytochrome P-450-dependent. This active metabolite, olmesartan, is a potent and selective AT_1 receptor antagonist, with no agonist activity.[1,2,3]

In healthy subjects, olmesartan has an elimination half-life of 12–18 hours, a value that is comparable to the longest half-lives of ARBs currently in clinical use.

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In a dose-ranging study, olmesartan was shown to be an effective once-per-day drug for the treatment of hypertension on the basis of ambulatory blood pressure measurements, and to have a safety profile similar to that of placebo.[4,5,6]

Although several previous studies have compared the antihypertensive efficacy of ARBs on the basis of cuff blood pressure change, such comparisons have largely been against losartan only.[7] Losartan is the first drug to be marketed within the ARB class and has been shown to be relatively ineffective for 24-hour control of blood pressure.

In the present study, we compared the efficacy of once-daily olmesartan with that of losartan, enalapril, and quinapril in patients with uncomplicated essential hypertension. All drugs were given at their recommended initial dosages. Blood pressure was evaluated with both cuff and ambulatory blood pressure monitoring (ABPM).[8,9]

Angiotensin-converting enzyme (ACE) inhibitors have been shown to be highly effective against a variety of cardiovascular disorders. A functional ACE system present in the vascular endothelium contributes to the regulation of vascular tone. The healthy endothelium releases autocrine and paracrine factors such as nitric oxide (NO) which maintain vascular integrity. Endothelial dysfunction occurs early in the course of atherosclerosis in response to cardiovascular risk factors and contributes to the morbidity of coronary disease.[10]

Angiotensin-converting enzyme inhibition has a favorable effect on endothelial function in animal models. Studies have suggested that bradykinin is the mediator responsible for the beneficial effects of ACE inhibition on endothelial function and atherosclerosis development. However, angiotensin II blockers, agents that have no effect on bradykinin, have demonstrated beneficial vascular effects comparable to ACE inhibitors in some studies.

Recently, six months of therapy with the tissue-specific ACE inhibitor, quinapril, has been shown to improve coronary endothelium-dependent vasodilation in patients with coronary atherosclerosis. The effect of angiotensin II blockade on endothelial function has not been studied in humans. In addition, the ACE gene I/D polymorphism is well described, and the deletion genotype has been associated with higher levels of circulating ACE. Some studies have suggested that the effects of ACE inhibition differ according to this gene polymorphism.[11,12]

MATERIALS AND METHODS:

PATIENTS: Male and female patients 18 years of age or older with essential hypertension were eligible for participation in this study. To be included, patients were required to have an average cuff diastolic blood pressure (DBP) of ≥100 and ≤115mm Hg and a mean daytime DBP of ≥90mm Hg and <120mm Hg, as measured by an ABPM device, after successful completion of a 4-week placebo run-in period.

Women were excluded from the study if they were nursing or were of child-bearing age and were not using a reliable means of birth control. Other exclusion criteria included any serious disorder that could limit the ability of the patient to participate in the trial, significant cardiovascular disease within the previous 6 months, and secondary hypertension.

No antihypertensive medications, other than the drugs used in the study, were allowed during the placebo run-in and active treatment phases of this trial. Patients were required to stop taking such medications at least 24 hours prior to receiving the first dose of placebo in the run-in phase of the study.

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Study Design: This randomized, double-blind, parallel-group, clinical trial was conducted after permission from institutional ethics committee. The study was divided into three phases: initial screening; 4-week single-blind placebo run-in; and 8-week double-blind active treatment. During the screening phase, patients signed an informed consent agreement and a medical history was taken.

A physical examination, 12-lead electrocardiography, and laboratory tests were performed. Patients fasted for a minimum of 8 hours prior to collection of blood and urine samples for laboratory testing. Sitting cuff blood pressure was measured with a mercury sphygmomanometer. For all cuff blood pressure measurements, patients were seated for a minimum of 5 minutes before the first measurement. Three recordings were taken, each separated by a minimum period of 1 minute. The pulse rate was measured once at the time of the second blood pressure reading.

Patients who met the entry criteria for the study during screening entered the 4-week single-blind placebo run-in phase of the study. Blood pressure and heart rate were measured at the end of each week of the run-in period (designated visits 1–4). If the daily average cuff DBP at both visits 3 and 4 was ≥100mg Hg and ≤115mm Hg, and if the difference between these two daily averages was ≤10mm Hg, the patient was considered eligible for ABPM.

ABPM was started in eligible patients immediately after the cuff blood pressure measurement at visit 4 and was continued for 24 hours. Patients with a mean daytime DBP of ≥90mm Hg and <120mm Hg by ABPM were eligible for randomization to treatment.

Patients entering the active treatment phase of the study were randomly assigned to receive a once-daily dose of one of the following ARBs: 20mg olmesartan; 50mg losartan; 10mg enalapril; or 20mg quinapril. All drugs were provided at the starting dose recommended by the manufacturer and were placed in identical capsules that matched the placebo capsules administered during the run-in phase of the study. All drugs were taken at breakfast except on examination days, when medication was not taken until after blood pressure had been measured.

Patients in the active treatment phase of the study were required to visit the clinic prior to taking their daily dose of medication 2, 4, and 8 weeks after commencing active treatment. At each visit, sitting cuff blood pressure was measured in triplicate, heart rate was measured, compliance was assessed by pill count, and patients were queried for adverse events. The ABPM measurement was repeated at week 8 only. If, at any visit, a patient had a mean daytime or average sitting cuff DBP that was ≥120mm Hg, or if the average sitting cuff systolic blood pressure (SBP) was =200mm Hg, the patient was removed from the study and treated with appropriate antihypertensive medication.

Acceptance Criteria for ABPM Data: The ABPM devices were programmed to record blood pressure every 15 minutes throughout a 24-hour period. Data acquired using ABPM were acceptable only if administration of medication occurred between 6:30 a.m. and 9:30 a.m. and were collected for a minimum period of 24 hours after administration of drugs. Within the 24-hour period, only hours with at least one reading were considered to be valid. Data from the entire 24-hour collection period were rejected if there were 6 or more nonconsecutive hours with no readings or 2 or more consecutive hours with no readings.

Statistical Design: The primary objective of this study was to assess the comparative efficacy of olmesartan, losartan, enalapril, and quinapril in terms of the reduction of elevated blood pressure. The primary efficacy variable was the change in sitting cuff DBP from baseline to the week 8 visit of the active treatment phase.

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The following parameters were secondary efficacy variables: change in sitting cuff DBP from baseline to the week 2 and 4 visits; change in sitting cuff SBP from baseline to the week 2, 4, and 8 visits; and change in mean 24-hour ambulatory DBP and SBP from baseline to week 8.

The duration and consistency of 24-hour blood pressure control were estimated by determining the DBP and SBP trough-to-peak ratios after 8 weeks of treatment. These ratios were calculated by determining the difference between the baseline and week 8 measurements for each hour of ABPM recording.

The resultant data followed the typical curves representative of circadian variation in blood pressure. Plots of the hourly mean values from each treatment group were fitted by application of a seven-term Fourier series. The trough-to-peak ratio was defined as the ratio of the lowest value of the fitted curve divided by the highest value of the fitted curve.

The required sample size of the treatment groups was estimated by assuming that the decrease in cuff sitting DBP during treatment with olmesartan would be 4.4, 3.8, and 3.0mm Hg greater than the decreases during treatment with losartan, enalapril, and quinapril, respectively. The values used in these calculations were taken from the results of parallel-design studies of similar duration to the present study.

Values for olmesartan were taken from previous registrational trials.[12] performed by given expected differences between drugs and standard deviations, and assuming an overall one-sided significance level of 0.05 and 90% power, 135 patients per treatment group were calculated to be required for this trial.

All efficacy analyses were performed on the intention-to-treat population, defined as any patient who had received at least one dose of study medication after randomization, and for whom baseline data and at least one post baseline measurement were available. If a patient discontinued treatment before the end of the study, the last measurement prior to removal from the trial was carried forward for analysis.

Baseline demographic characteristics were summarized and compared among treatment groups. Categorical variables were analyzed by the X^2 test and continuous variables were tested with analysis of variance (ANOVA), with treatment used as a factor. The changes in blood pressure that occurred within each treatment group during the study were analyzed with paired t-tests. A probability (p) of =0.05 was considered significant for these analyses.

Differences among treatment groups in the primary efficacy variable (Change in cuff DBP over the 8 weeks of treatment) were analyzed with an analysis of covariance (ANCOVA) model, with baseline as the covariate and treatment and center as factors. The primary statistical comparisons were between olmesartan and each of the three comparison drugs. One-sided tests were used to compare the least squared means computed from ANCOVA models.

To ensure that the overall significance level remained at 5%, p values were adjusted with a multiple-test procedure. A similar ANCOVA model was used for all other comparisons of cuff blood pressure, and for comparisons of ambulatory blood pressure. All subsequent references to means refer to least squared means rather than unadjusted raw means.

Safety: All adverse events reported by patients or observed by investigators during any stage of the trial were recorded and assessed for seriousness and relation to the study drug. The results of all laboratory tests were assessed by the investigators for clinical significance and for possible

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relationship to the study drug. Adverse event data are presented for the period of active treatment only and all randomized patients are included.

The clinical and laboratory adverse event data were examined by Fisher's exact test for differences among treatment groups. Clinically significant changes in physical examination findings that occurred between screening and the end of the study were also recorded.

RESULTS:

Patient Disposition: A total of 234 patients were screened for participation in the trial. Of these, 200 patients entered the treatment phase of the study and were randomized to olmesartan (n=50), losartan (n=50), valsartan (n=50), or irbesartan (n=50). The most common reasons for discontinuation prior to randomization were failure to meet the blood pressure entry criteria (70%) and patient request (9%). The percentage of patients in each group who completed the entire 8 weeks of the study were 93.2%, 91.3%, 91.0%, and 95.9% for olmesartan, losartan, enalapril, and quinapril, respectively.

Baseline Demographics: The demographic characteristics of the intent-to-treat population for cuff analysis of blood pressure are shown in Table I. There were no significant differences in the demographics of the different treatment groups. All groups were predominantly white, approximately 62% male, and the mean age of all groups was approximately 52 years. The average patient had stage 2 hypertension according to DBP. In all treatment groups, baseline DBP was approximately 104mm Hg and baseline SBP approximately 157mm Hg.

Table I. Summary of Baseline Demographic Characteristics and Blood Pressure of Patients in the Intent-to-Treat Population

	Olmesartan	Losartan	Enalapril	Quinapril
N	50	50	50	50
Age (years)	52.4±8.95	51.6±9.30	51.7±9.62	51.9±9.63
Other	11.0	17.8	13.3	16.5
Gender (%)				
Male	66.9	62.3	57.7	58.6
Female	33.1	37.7	42.3	41.4
Baseline blood pressure				
Cuff DBP	104±3.5	104±3.5	104±3.3	104±3.6
Cuff SBP	157±13.3	157±11.9	155±12.1	156±12.8

All values are means±SD. DBP=diastolic blood pressure; SBP=systolic blood pressure

Cuff Blood Pressure and Heart Rate: Treatment with all four ARBs resulted in significant decreases in both cuff DBP and SBP from baseline after 8 weeks of treatment ($p<0.001$ for all groups). The mean reduction in cuff DBP achieved with olmesartan (13.5mm Hg) was significantly greater than that with losartan (8.2mm Hg; $p=0.0002$), enalapril (7.9mm Hg; $p<0.0001$), or quinapril (9.9mm Hg; $p=0.0412$) (Figure I). Over the 8-week treatment period, therapy with olmesartan also resulted in a mean reduction of SBP of 11.3mm Hg.

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Patients treated with losartan, enalapril, and quinapril achieved mean SBP reductions of 9.5, 8.4, and 11.0mm Hg, respectively, over the same period. These differences were not statistically significant at 8 weeks.

Figure 1: Least squares mean change from baseline in cuff diastolic blood pressure (DBP) after 8 weeks of treatment with olmesartan, losartan, enalapril, and quinapril. *p<0.05 vs. olmesartan; †p<0.0005 vs. olmesartan.

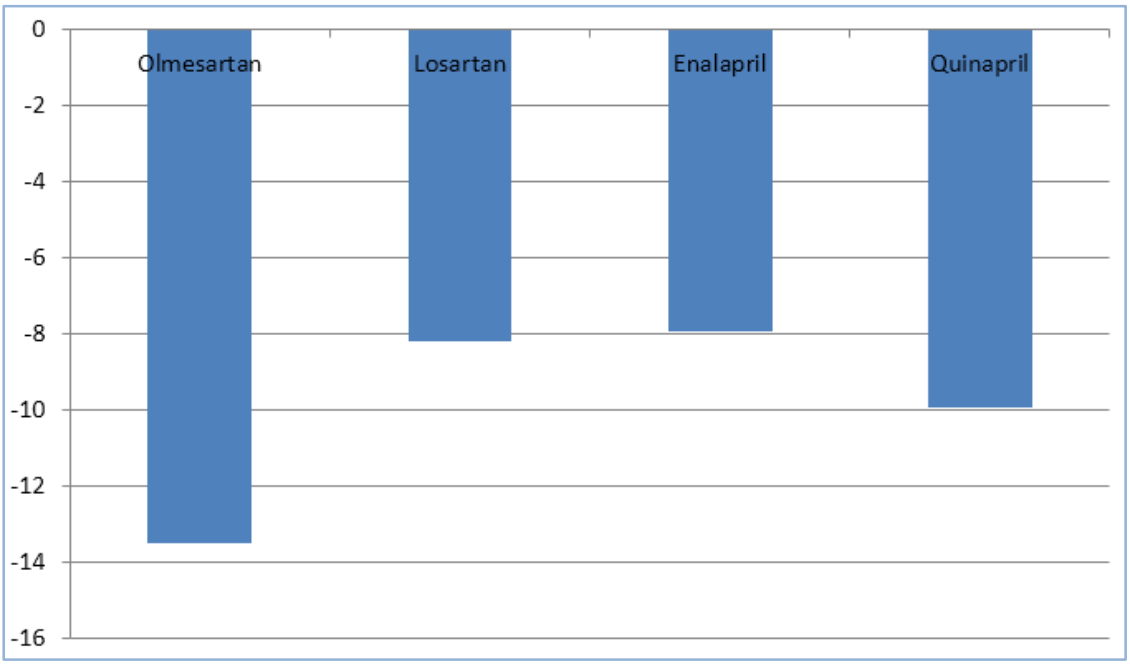

Figure 1

The differences in cuff blood pressure reduction after treatment with olmesartan and each of the three comparison drugs were apparent within 2 weeks (Table II). At this time, the mean DBP of the olmesartan-treated group had decreased by 10.7mm Hg, while treatment with losartan had resulted in a mean decrease of 7.6mm Hg, and both the enalapril- and quinapril -treated patients showed a mean decrease of 9.0mm Hg. Similar differences in DBP reduction among the treatment groups were evident in the week 4 data (Table II).

The differences in DBP response between olmesartan and the comparison drugs were significant for all comparisons at both 2 and 4 weeks. Olmesartan was also significantly more effective than all three comparison drugs in reducing SBP after 2 weeks but not at 4 weeks of treatment (Table II).

At 2 weeks mean SBP was reduced by 13.0 mm Hg in the olmesartan-treated group, compared with 8.9mm Hg in the losartan group (p=0.001), 9.2mm Hg in the enalapril group (p=0.003), and 10.8 mm Hg in the quinapril group (p=0.050). At week 4, the changes in SBP with olmesartan and the comparison drugs were not significantly different. None of the ARBs used in this study resulted in any significant change in heart rate.

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Table II. Change in Cuff DBP and SBP After 2 and 4 Weeks of Treatment

	Olmesartan	Losartan	Enalapril	Quinapril
		2 Weeks		
Δ DBP	−10.7	−7.6†	−9.0*	−9.0*
Δ SBP	−13.0	−8.9**	−9 2**	−10.8*
		4 Weeks		
Δ DBP	−11.4	−8.9†	−9.7*	−9.9*
Δ SBP	−13.4	−11.4	−10.6	−13.2

Least squares mean change from baseline in cuff diastolic blood pressure (DBP) and systolic blood pressure (SBP) after 2 and 4 weeks of treatment with olmesartan, losartan, valsartan, and irbesartan. *p=0.05 vs. olmesartan; **p=0.005 vs. olmesartan; †p=0.0005 vs. olmesartan

Ambulatory Blood Pressure Monitoring: The results of the 24-hour ABPM measurements after 8 weeks of treatment are shown in Figure 2.

The overall results were similar to those obtained with cuff blood pressure measurements. The reduction in mean 24-hour DBP with olmesartan (8.5mm Hg) was significantly greater than the reduction obtained with losartan and enalapril (6.2 and 5.6mm Hg, respectively) and showed a trend toward significance when compared to the reduction in DBP seen with quinapril (7.4mm Hg; p=0.087).

Figure 2: Change in least squares mean 24-hour diastolic (DBP) and systolic blood pressure (SBP) from baseline after 8 weeks of treatment with olmesartan, losartan, enalapril, and quinapril. *p<0.05 vs. olmesartan.

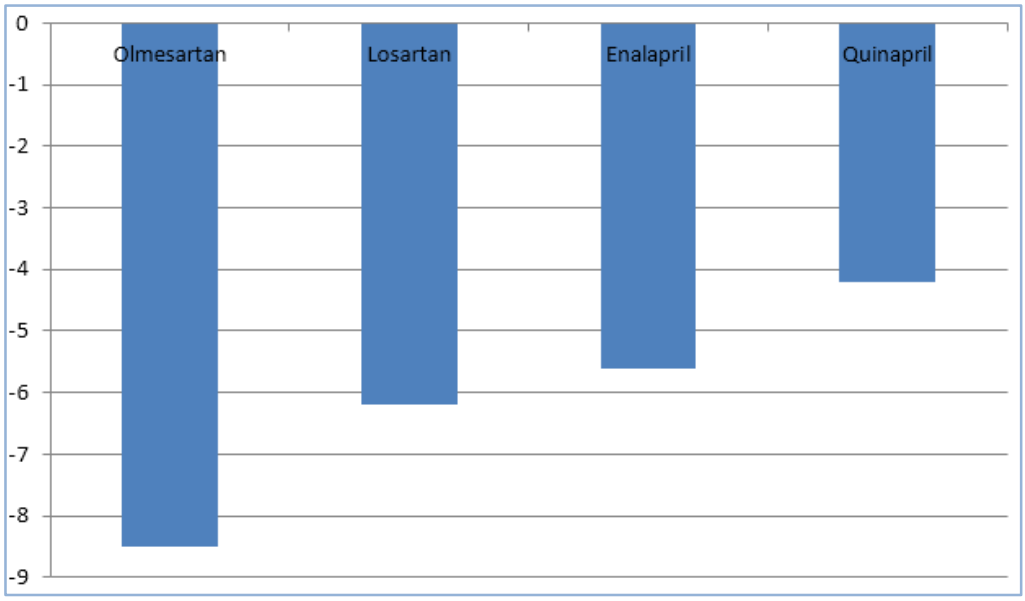

Figure 2

A similar pattern of difference was evident in the ambulatory SBP data. Olmesartan reduced mean 24-hour SBP by 12.5 mm Hg after 8 weeks. This decrease was significantly greater than the

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reduction achieved by losartan and enalapril (9.0 and 8.1mm Hg, respectively) but not statistically different from the reduction with quinapril (11.3mm Hg).

Changes in mean daytime and nighttime DBP and SBP, as measured by ABPM after 8 weeks of treatment with the various ARBs, are shown in (Table III) For purposes of these measurements, daytime was defined as 8:00 a.m. to 7:59 p.m. and nighttime as 8:00 p.m. to 7:59 a.m. Treatment with olmesartan for 8 weeks resulted in a reduction of both mean daytime DBP and SBP (10.2 and 14.7 mm Hg, respectively) that was significantly larger than the reductions seen with losartan and enalapril but not significantly different from that seen with quinapril.

Table III. Change in Mean Daytime and Nighttime ABPM, DBP, and SBP After 8 Weeks of Treatment With Olmesartan, Losartan, Enalapril, or Quinapril

	Olmesartan	Losartan	Enalapril	Quinapril
		Day		
Δ DBP	−10.2	−7.2**	−7.0†	−8.8
Δ SBP	−14.7	−10.9**	−10.2**	−13.8
		Night		
Δ DBP	−6.8	−5.2	−4.2**	−5.9
Δ SBP	−10.3	−7.3*	−6.1**	−8.8

ABPM=ambulatory blood pressure monitoring; DBP=diastolic blood pressure; SBP=systolic blood pressure *p=0.05 vs. olmesartan; **p=0.005 vs. olmesartan; †p=0.0005 vs. olmesartan

All of the ARBs in this study had less effect on blood pressure during the night than during the day. The drop in mean nighttime DBP with olmesartan treatment (6.8mm Hg) was statistically greater than the nighttime DBP reduction with enalapril and similar to the reductions with losartan and quinapril. The reduction from baseline in nighttime SBP after 8 weeks of olmesartan (10.3mm Hg) was significantly greater than the reductions with losartan (7.3mm Hg) and enalapril (6.1mm Hg) and similar to the drop in nighttime SBP with quinapril (8.8mm Hg).

Trough-to-Peak Ratios: The stability of blood pressure control achieved with each treatment during the 24-hour between-doses period was also assessed by determination of the systolic and diastolic trough-to-peak ratios from the week 8 ABPM data. For SBP, this ratio was highest for olmesartan (0.69). Losartan, enalapril, and quinapril achieved SBP trough-to-peak ratios of 0.64, 0.55, and 0.62, respectively. For DBP, the trough-to-peak ratios of olmesartan and losartan were similar (0.68 and 0.69, respectively), and higher than those for enalapril (0.48) and quinapril (0.60). Trough-to-peak ratios from the four treatment groups were not compared statistically.

Safety: The overall incidence of adverse events was comparable among the four treatment groups. In this study, 30.6% (n=45) of the patients treated with olmesartan experienced at least one clinical adverse event. This compares with 32.0% (n=48) of the losartan group, 44.8% (n=65) of the enalapril group, and 35.6% (n=52) of the quinapril group (Table IV). Upper respiratory infection, headache, fatigue, back pain, and dizziness were the most common complaints. Serious adverse events occurred in a total of four patients after randomization (Olmesartan, n=1; losartan, n=1; enalapril, n=2). In the opinion of the investigator, these events were not related to the study drugs.

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Table IV. Adverse Events During the Active Treatment Period

	Olmesartan n=147	Losartan n=150	Enalapril n=145	Quinapril n=146
	n(%)			
Patients with ≥1 AE during active treatment				
Total AEs	45 (30.6)	48 (32.0)	65 (44.8)	52 (35.6)
Drug-related AEs*	12 (8.2)	14(9.3)	13 (9.0)	11 (7.5)
Serious AEs (total)	1 (0.7)	1(0.7)	2(1.4)	0(0.0
Severe AEs (total)	4 (2.7)	2(1.3)	3(2.1)	3(2.1)
Total AES in ≥2% of patients in any treatment group				
URT infection	4 (2.7)	4 (2.7)	12(8.3)	8(5.5)
Headache	7(4.8)	6 (4.0)	6(4.1)	8(5.5)
Fatigue	3 (2.0)	5 (3.3)	3 (2.1)	2(1.4)
Back pain	1 (0.7)	5 (3.3)	3 (2.1)	2(1.4)
Dizziness	2(1.4)	1 (0.7)	2(1.4)	5 (3.4)
Diarrhea	2(1.4)	1 (0.7)	1 (0.7)	5 (3.4)
Arthralgia	1 (0.7)	3 (2.0)	3 (2.1)	1 (0.7)

Table V. Adverse Events During the Active Treatment Period

	Olmesartan n=147	Losartan n=150	Enalapril n=145	Quinapril n=146
	n(%)			
Coughing	3 (2.0)	1 (0.7)	2(1.4)	1 (0.7)
Pharyngitis	0 (0.0)	4 (2.7)	1 (0.7)	1 (0.7)
Influenza-like symptoms	1 (0.7)	0 (0.0)	1 (0.7)	4 (2.7)
Myalgia	0 (0.0)	1 (0.7)	4 (2.8)	0 (0.0)
Toothache	0 (0.0)	0 (0.0)	4 (2.8)	1 (0.7)
Peripheral edema	1 (0.7)	0 (0.0)	3(2.1)	1 (0.7)
Migraine	0 (0.0)	3 (2.0)	0 (0.0)	0 (0.0)

AE=adverse event; URT=upper respiratory tract; *adverse events considered by the investigator to be definitely, probably, or possibly related to study drug administration

Laboratory adverse events occurred in a total of 21 randomized patients during the period of active treatment. Eight of these patients received olmesartan (5.4%), five losartan (3.3%), five enalapril (3.4%), and three quinapril (2.1%). There were no significant differences among groups in the overall incidence of laboratory adverse events, or in the incidence of adverse events within any body system.

Four patients (Two losartan, two valsartan) had elevations of alanine aminotransferase or aspartate aminotransferase of >3x the upper limit of normal or >3x the baseline value, if the baseline value was above the normal range. One of these patients had elevated alanine aminotransferase and γ-glutamyl transferase levels prior to study treatment; the elevations in two patients decreased after the end of study treatment; and one patient did not have follow-up levels tested (the investigator did not consider the elevations to be significant).

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A total of seven patients discontinued the study after randomization as a result of clinical or laboratory adverse events (Olmesartan, n=2; enapril, n=4; quinapril, n=1). Two of these adverse events were deemed possibly related to treatment (fatigue and malaise [olmesartan] and cough [enalapril]).

Endothelial Function and ACE-inhibition: Angiotensin converting enzyme–inhibition is thought to improve vascular function by several mechanisms.[13,14] It decreases the concentration of angiotensin II and hence endothelin, increases the concentration of bradykinin, which is a vasodilator and stimulator of NO, endothelial derived hyperpolarizing factor and prostacyclin, and decreases superoxide anion concentration.

An augmentation of endothelium-dependent vasodilation has been demonstrated for several ACE inhibitors in animal studies. In the recently published TREND (Trial on Reversing Endothelial Dysfunction) study, six months of therapy with quinapril (40mg/day) attenuated acetylcholine-induced vasoconstriction in patients with coronary disease. Hornig et al. have recently demonstrated that the acute arterial administration of quinapril at augmented brachial FMD, and that this effect is predominantly mediated via the bradykinin-2 receptor. Animal studies had also suggested that the beneficial vascular effect of ACE inhibition was mediated through bradykinin and NO.[15,16]

It is not clear from the present study why augmentation of FMD was seen with quinapril but not enalapril. Although the improvement from baseline was not statistically different among the drugs tested, only quinapril showed a difference from baseline, and there was a trend for a difference between the two ACE inhibitors (p=0.12).

The lack of effect of enalapril, losartan and amlodipine may be related to choice of dose or length of treatment. However, quinapril has been shown to have high tissue specificity for ACE, and the dissociation of the drug from the enzyme is markedly prolonged compared with other converting enzyme inhibitors.

In addition, the enhanced lipophilicity of the drug may allow better cellular penetration with beneficial effects on enzymatic processes such as cNOS activity, for example. Greater inhibition of vascular ACE has also been demonstrated for quinapril compared with enalapril in a recent human study of forearm blood flow. A more recent study by Hornig et al. demonstrated improved FMD acutely in response to quinaprilat but not to increasing doses of enalaprilat in patients with heart failure.[17,18]

Studies of enalapril in diabetics with endothelial dysfunction have shown mixed results. One month of treatment with enalapril was able to improve forearm blood flow in response to acetylcholine in patients with type I diabetes, whereas 24 weeks of enalapril had no statistically significant effect on FMD in other patients with type I diabetes. Further work is required to contrast the effects of different ACE inhibitors on vascular function in different disease states.[19,20]

Endothelial Function and ACE Genotype*:* Polymorphism of the ACE gene has been demonstrated, and the presence of the deletion allele has been associated with higher levels of circulating and tissue ACE. The DD genotype has also been associated with increased risk of coronary restenosis and myocardial infarction in some but not all studies.

In addition, some studies have suggested a relationship between the genotype and physiological effects from ACE inhibition with attenuation of beneficial effect noted with the deletion allele.

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In the present study we noted no difference in baseline brachial FMD between the different genotypes, as was seen in one other study. However, the improvement in FMD with quinapril was restricted to the ID and II genotypes.

The reason for this observation is not explained by this study. It may relate to increased tissue levels of ACE, attenuated interaction with quinapril and the tissue ACE, or increased levels of oxidative stress in these subjects.

Down-regulation of the AT1 receptor in those with the DD genotype has also been recently suggested. The duration of effect of ACE inhibitors may also be related to the genotype, affecting the results seen.[21]

Endothelial Function and Angiotensin-Ii Blockade: Farhy and colleagues demonstrated that both ramipril and losartan reduced neointimal proliferation in a rat balloon injured model, but that ramipril was more effective. Concomitant bradykinin blockade with HOE-140 nullified this advantage, suggesting that kinins were important in the beneficial effect of ramipril in this model.

However, a similarly designed study in rabbits comparing perindopril and losartan demonstrated equal efficacy in reducing neointimal formation.

This is the first human study to assess endothelial function with an angiotensin-II receptor blocker in humans. Although there was no difference in the response between quinapril and losartan, losartan did not augment FMD from baseline in our study. Although this might suggest that vasodilator kinins are important in augmenting endothelium-dependent vasodilation, further studies are required to clarify the impact of angiotensin-II blockade on endothelial function.[22]

DISCUSSION:

Cuff Blood Pressure: Although several previous head-to-head comparisons of ARBs in which cuff blood pressure was used as the primary efficacy variable have been published, all of the previous studies were comparisons with only losartan, the first ARB marketed. The present study is the first to include more than two ARBs at recommended starting doses and to directly compare the antihypertensive efficacy of more recently introduced ARBs.

The principal finding of this study is that treatment with a starting dose of olmesartan results in a significantly greater reduction of cuff DBP, the primary efficacy variable of this trial, than treatment with starting doses of losartan, enalapril, and quinapril. The superior efficacy of olmesartan in reducing cuff DBP was evident 2 weeks after the initiation of treatment, and was maintained for the duration of the trial.

As with the change in DBP, the olmesartan-induced reduction in SBP was rapid in onset. Patients treated with olmesartan experienced a mean reduction in cuff SBP of 13.0mm Hg after 2 weeks of treatment. Mean reductions achieved in the three comparison groups at 2, but not 4 weeks, were significantly lower, ranging from 8.9mm Hg (losartan) to 10.8mm Hg (quinapril). The efficacy of olmesartan was maintained at 4 and 8 weeks (reductions of 13.4 and 11.3mm Hg, respectively), although the comparisons with losartan, enalapril, and quinapril did not achieve statistical significance at these time periods.

The greater efficacy of olmesartan in reducing trough cuff DBP may be related to its relatively long half-life (12–18 hours).[4] Of the three comparison drugs used in the current study, quinapril has the longest half-life (11–15 hours); the half-lives of losartan (2 hours), the active metabolite of losartan, EXP3174 (4–5 hours), and enalapril (6 hours) are all substantially shorter.

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Since a longer half-life is associated with a longer duration of action, this difference in pharmacokinetics may partially explain the differences in efficacy among these four ARBs. As a corollary, the long half-life of drugs such as olmesartan and quinapril may minimize the effect of missed or delayed dosing of medication.

A substantial proportion of patients are erratic in the time of day at which they take once-daily antihypertensive medication, and this inconsistency in dosing interval is associated with less effective control of blood pressure.

Ambulatory Blood Pressure: ABPM is the most reliable way to test the 24-hour efficacy of an antihypertensive agent. The use of ABPM criteria for diagnosis of hypertension permits elimination of patients with white-coat hypertension from clinical trials of hypertension and provides a continuous record of blood pressure during the normal daily activities of the patient.

Ambulatory blood pressure has been used as a primary efficacy variable in several previous head-to-head comparisons of the antihypertensive effectiveness of ARBs. All of these studies involved direct comparison of the effects of two ARBs on ambulatory blood pressure and in all but one of these studies, one of the ARBs was losartan. The present study, by contrast, is the first to compare antihypertensive efficacy as measured by ABPM in more than two ARBs in head-to-head fashion.

The results of the present study demonstrated that olmesartan is more effective than enalapril and losartan in reducing mean 24-hour ambulatory DBP and SBP after 8 weeks of treatment. Similar reductions in mean ambulatory DBP and SBP were seen after treatment with olmesartan and quinapril. This pattern of antihypertensive superiority to losartan and enalapril, and similarity to quinapril, was also seen in both the daytime and nighttime ABPM measurements.

Magnitude of Blood Pressure Differences among Treatments: Relationship with Outcome Available data suggest that the small differences in DBP reduction between olmesartan and the other ARBs in this study (Approximately 2-4mm Hg), sustained over time, may be associated with reductions in the risk of cardiovascular events. In a comprehensive overview of nine prospective observational studies involving 420,000 individuals, MacMahon et al. concluded that a reduction in DBP of 5mm Hg is associated with reductions of at least 21% in the incidence of coronary heart disease and at least 34% in the incidence of stroke.

More recently, in the Hypertension Optimal Treatment (HOT) trial, there were 28% fewer myocardial infarctions in the treatment group with a target DBP of =80mm Hg than in the group with a target DBP of =90mm Hg, although the actual difference in mean DBP achieved by these two groups was only 4.1mm Hg. A similarly strong association between the risk of adverse cardiovascular events and both DBP and SBP has also been demonstrated in special populations, such as patients with diabetes. Observations such as these suggest that the significant differences in DBP reduction with olmesartan compared to the other ARBs in the present study may be of clinical value.

As with DBP, elevations in SBP are associated with increased risk of coronary heart disease, stroke, myocardial infarction, occlusive peripheral arterial disease, and congestive heart failure.

A number of studies have quantified the change in risk of adverse cardiovascular outcomes associated with specific changes in SBP. Kannel found that men with SBP of 140–159mm Hg were at 50%–75% greater risk of cardiovascular disease than men with SBP of 120–139mm Hg. In a meta-analysis of eight trials carried out in elderly patients with isolated systolic hypertension, Staessen et al. found that the relative risks of cardiovascular events, cardiovascular deaths, stroke, and all-cause

mortality increased by 15%, 22%, 22%, and 26%, respectively, for each 10mm Hg increase in initial SBP.

These observations suggest that the ARB-induced reductions in cuff SBP of the magnitude seen in the present study are very likely to be of clinical significance.

Trough-to-Peak Ratio: The trough-to-peak ratio is a measure of the consistency of the anti-hypertensive efficacy of a drug during the entire dosing interval. It is an important parameter because increased blood pressure variability is associated with increased risk of end-organ damage in hypertensive patients. An optimal antihypertensive formulation should provide 24-hour efficacy with a once-daily dose, with at least 50% of the peak effect remaining after 24 hours.

Lower ratios may reflect excessive and potentially detrimental decreases in blood pressure at peak, poor control of hypertension at trough, or excessive variability of pharmacologic effect. This parameter is also of therapeutic importance if patients miss a dose of medication. All of the agents assessed in this study had trough-to-peak ratios for both DBP and SBP that were well above 0.5, with the exception of valsartan, which had a diastolic trough-to-peak ratio of 0.48.

Safety: There were no differences among treatment groups in the incidence of clinical or laboratory adverse events. Serious and severe adverse events were rare in all groups. As a class, ARBs are noted for having a side effect profile similar to that of placebo. A placebo group was not included in the current study, but the total adverse event rate (Which ranged from 31% for olmesartan to 45% for enalapril) is similar to that reported for the placebo group in several placebo-controlled trials carried out in hypertensive patients. Headache, which is often one of the most common adverse events in studies involving hypertensive patients, frequently has a lower incidence in patients treated with ARBs than in those treated with placebo. Wiklund et al. showed that the incidence of headache was reduced after 6 months of antihypertensive treatment in all three target groups in the HOT trial, a finding that supports the conclusion that lowering elevated blood pressure reduces the incidence of headache in hypertensive patients.

CONCLUSION: This study has shown that the reduction in cuff DBP resulting from 8 weeks of treatment with olmesartan is greater than that seen following treatment with losartan, enalapril, or quinapril. Olmesartan also produced a reduction in cuff SBP that was numerically greater than, but not statistically significantly different from, that achieved by the three comparison drugs. The observation made in several clinical trials that small differences in both DBP and SBP are associated with substantial reductions in the incidence of major cardiovascular events suggests that small differences in blood pressure reduction between ARBs may have important long-term effects.

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