COMPARATIVE ANALYSIS OF EFFICACY AND SAFETY OF LOSARTAN, OLMESARTAN, TELMISARTAN AND VALSARTAN IN PATIENTS WITH HYPERTENSION

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ABSTRACT

BACKGROUND
Angiotensin II Receptor Blockers (ARBs) are the newest class of approved antihypertensive agents and the important class of drugs to exert their primary antihypertensive action by interrupting the renin-angiotensin system.

Objectives - It was randomised, double-blind trial in which efficacy of olmesartan (20 mg once a day) and losartan (50 mg once a day), telmisartan 40 mg OD and Valsartan 80 mg OD 1 hour before meal was compared in patients with hypertension. It was assessed in patients with a cuff Diastolic Blood Pressure (DBP) between 100 to 115 mmHg and a mean day time DBP between 90 to 120 mmHg when measured by Ambulatory Blood Pressure Monitoring (ABMP).

MATERIALS AND METHODS
Cuff and ambulatory blood pressures were monitored at baseline and after 8 weeks of treatment. All groups were adults and approximately 62% male and the mean age was 52 years. In all groups, mean baseline DBP and Systolic Blood Pressure (SBP) was approximately 104 and 157 mmHg respectively. The reduction of sitting cuff DBP with Losartan (13.5 mmHg), the primary efficacy variable of this study was significantly greater than with olmesartan, telmisartan and valsartan (8.2, 7.9 and 9.9 mmHg, respectively). Reductions of cuff SBP with the four ARBs ranged from 8.4–13.3 mm Hg and were not significantly different. The reduction in mean 24-hour DBP with Losartan (8.5 mmHg) was significantly greater than reductions with Olmesartan and Telmisartan (6.2 and 5.6 mmHg, respectively) and showed a trend toward significance when compared to the reduction in DBP with Valsartan (7.4 mmHg; p=0.087). The reduction in mean 24-hour SBP with Losartan (12.5 mmHg) was significantly greater than the reductions with Olmesartan and Telmisartan (9.0 and 8.1 mmHg, respectively) and equivalent to the reduction with Valsartan (11.3 mmHg). All drugs were well tolerated.

RESULTS
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 randomised to Losartan (n = 50), olmesartan (n = 50), telmisartan (n = 50) or valsartan (n = 50). The most common reasons for discontinuation prior to randomisation 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 Losartan, olmesartan, telmisartan and valsartan respectively. The differences in cuff blood pressure reduction after treatment with Losartan and each of the three comparison drugs were apparent within 2 weeks. The mean DBP of the Losartan treated group had decreased by 10.7 mmHg, while treatment with Olmesartan had resulted in a mean decrease of 7.6 mmHg and both the telmisartan and valsartan treated patients showed common mean decrease of 9.0 mmHg.

CONCLUSION
Losartan, at its starting dose, is more effective than the starting doses of the other tested drugs like olmesartan, telmisartan and valsartan in reducing cuff DBP in patients with essential hypertension.

KEYWORDS
Essential Hypertension, Losartan, Olmesartan, Telmisartan, Valsartan.


BACKGROUND
Angiotensin II Receptor Blockers (ARBs) are the newest class of approved antihypertensive agents and the important class of drugs to exert their primary antihypertensive action by interrupting the renin-angiotensin aldosterone system. ARBs prevent the hypertensive effects of angiotensin II by selective blockade of the angiotensin II type 1 (AT1) receptor.

Olmesartan is a newer ARB that was discovered during a systematic survey of the AT1 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 AT1 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. 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.\textsuperscript{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.\textsuperscript{7}  

Endothelial dysfunction occurs early in the course of atherosclerosis in response to cardiovascular risk factors and contributes to the morbidity of coronary disease.\textsuperscript{8} Angiotensin-converting enzyme inhibition has a favourable effect on endothelial function in animal models.\textsuperscript{8} 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.

**MATERIALS AND METHODS**  
Adult 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 ≤ 115 mmHg and a mean daytime DBP of ≥ 90 mmHg and < 120 mmHg 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.

This randomised, double blind, parallel group, clinical trial was conducted after permission from Institutional Ethics Committee. The randomisation was done by random number table with the help of statistician. 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 ≥ 100 mmHg and ≤ 115 mmHg, and if the difference between these two daily averages was ≤ 10 mmHg, 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 ≥ 90 mmHg and < 120 mmHg by ABPM were eligible for randomisation 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: 20 mg olmesartan; 50 mg losartan; 20 mg telmisartan; or 80 mg valsartan. All drugs were provided at the starting recommended dose 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 the patient had a mean daytime or average sitting cuff DBP that was ≥ 120 mmHg or if the average sitting cuff Systolic Blood Pressure (SBP) was 200 mmHg, 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 non-consecutive 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 Losartan, olmesartan, telmisartan, valsartan 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. 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 Losartan would be 4.4, 3.8 and 3.0 mmHg greater than the decreases during treatment with olmesartan, telmisartan and valsartan respectively. The 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 analysis was performed on the intention-to-treatment population, defined as any patient who had received at least one dose of study medication after randomisation 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 summarised and compared among treatment groups. Categorical variables were analysed by the chi square 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 analysed with paired t-tests. A probability (p) of 0.05 was considered significant.6

Differences among treatment groups in the primary efficacy variable (change in cuff DBP over the 8 weeks of treatment) were analysed with an Analysis of Covariance (ANCOVA) model with baseline as the covariate and treatment and center as factors. 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 relationship to the study drug. Adverse event data are presented for the period of active treatment only and all randomised 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
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 randomised to Losartan (n = 50), olmesartan (n = 50), telmisartan (n = 50) or valsartan (n = 50). The most common reasons for discontinuation prior to randomisation 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 losartan, olmesartan, telmisartan and valsartan respectively.

Baseline Demographics
There were no significant differences in the demographics of the different treatment groups. Gender ratio was 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 104 mmHg and baseline SBP approximately 157 mmHg.

<table>
<thead>
<tr>
<th>Losartan</th>
<th>Olmesartan</th>
<th>Telmisartan</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.4±8.95</td>
<td>51.6±9.30</td>
<td>51.7±6.62</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>Male 66.9</td>
<td>62.3</td>
<td>57.7</td>
</tr>
<tr>
<td></td>
<td>Female 33.1</td>
<td>37.7</td>
<td>42.3</td>
</tr>
<tr>
<td>Cuff DBP</td>
<td>104±3.5</td>
<td>104±3.5</td>
<td>104±3.3</td>
</tr>
<tr>
<td>Cuff SBP</td>
<td>157±11.3</td>
<td>157±11.9</td>
<td>155±12.1</td>
</tr>
<tr>
<td>All values are means±SD</td>
<td></td>
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</tbody>
</table>

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

Cuff Blood Pressure and Heart Rate
Treatment with ARBs resulted in significant decreases in both cuff DBP and SBP from baseline after 8 weeks of treatment (p < 0.001 for both groups). The mean reduction in cuff DBP achieved with Losartan (13.5 mmHg) was significantly greater than that with olmesartan (8.2 mmHg; p = 0.0002), telmisartan (7.9 mmHg; p < 0.0001) or valsartan (9.9 mmHg; p = 0.0412) (Figure I). Over the 8-week treatment period, therapy with losartan also resulted in a mean reduction of SBP of 11.3 mmHg. Patients treated with olmesartan, telmisartan and valsartan achieved mean SBP reductions of 9.5, 8.4 and 11.0 mmHg 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 Losartan, Olmesartan, Telmisartan and Valsartan, p<0.05

The differences in cuff blood pressure reduction after treatment with Losartan and each of the three comparison drugs were apparent within 2 weeks (Table II). At this time,
the mean DBP of the Losartan treated group had decreased by 10.7 mmHg, while treatment with Olmesartan had resulted in a mean decrease of 7.6 mmHg and both the telmisartan and valsartan treated patients showed a mean decrease of 9.0 mmHg. Similar differences in DBP reduction among the treatment groups were evident in the week 4 data (Table II). The differences in DBP response between Losartan and the comparison drugs were significant for all comparisons at both 2 and 4 weeks. Losartan 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 mmHg in the Losartan-treated group compared with 8.9 mmHg in the olmesartan group (p = 0.001), 9.2 mmHg in the telmisartan group (p = 0.003) and 10.8 mmHg in the valsartan 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.

<table>
<thead>
<tr>
<th>Losartan</th>
<th>Olmesartan</th>
<th>Telmisartan</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ DBP</td>
<td>−10.7</td>
<td>−7.6†</td>
<td>−9.0*</td>
</tr>
<tr>
<td>Δ SBP</td>
<td>−13.0</td>
<td>−8.9**</td>
<td>−9.2**</td>
</tr>
<tr>
<td>2 Weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ DBP</td>
<td>−11.4</td>
<td>−8.9†</td>
<td>−9.7*</td>
</tr>
<tr>
<td>Δ SBP</td>
<td>−13.4</td>
<td>−11.4</td>
<td>−10.6</td>
</tr>
</tbody>
</table>

Table II. Change in cuff DBP and SBP after 2 and 4 weeks of treatment.

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, enalapril, and quinapril; †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 Losartan (8.5 mmHg) was significantly greater than the reduction obtained with olmesartan and telmisartan (6.2 and 5.6 mmHg, respectively) and showed a trend toward significance when compared to the reduction in DBP seen with valsartan (7.4 mmHg; p = 0.087).

A similar pattern of difference was evident in the ambulatory SBP data. Losartan reduced mean 24-hour SBP by 12.5 mmHg after 8 weeks. This decrease was significantly greater than the reduction achieved by olmesartan and (9.0 and 8.1 mmHg, respectively), but not statistically different from the reduction with valsartan (11.3 mmHg). 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 losartan for 8 weeks resulted in a reduction of both mean daytime DBP and SBP (10.2 and 14.7 mmHg, respectively) that was significantly larger than the reductions seen with olmesartan and telmisartan, but not significantly different from that seen with valsartan.

<table>
<thead>
<tr>
<th></th>
<th>Losartan</th>
<th>Olmesartan</th>
<th>Telmisartan</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ DBP</td>
<td>−10.2</td>
<td>−7.2**</td>
<td>−7.0†</td>
<td>−8.8</td>
</tr>
<tr>
<td>Δ SBP</td>
<td>−14.7</td>
<td>−10.9**</td>
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<td>−13.8</td>
</tr>
<tr>
<td>Night</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ DBP</td>
<td>−6.8</td>
<td>−5.2</td>
<td>−4.2**</td>
<td>−5.9</td>
</tr>
<tr>
<td>Δ SBP</td>
<td>−10.3</td>
<td>−7.3*</td>
<td>−6.1**</td>
<td>−8.8</td>
</tr>
</tbody>
</table>

Table III. Change in mean daytime and nighttime ABPM, DBP and SBP after 8 weeks of treatment with Losartan, Olmesartan, Telmisartan or Valsartan

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

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 losartan treatment (6.8 mmHg) was statistically greater than the nighttime DBP reduction with telmisartan and similar to the reductions with olmesartan and valsartan. The reduction from baseline in nighttime SBP after 8 weeks of losartan (10.3 mmHg) was significantly greater than the reductions with olmesartan (7.3 mmHg) and telmisartan (6.1 mmHg) and similar to the drop in nighttime SBP with valsartan (8.8 mmHg).10

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 ratio. For SBP, this ratio was highest for losartan (0.69). Olmesartan, telmisartan and valsartan achieved SBP trough-to-peak ratios of 0.64, 0.55 and 0.62, respectively. For DBP, the trough-to-peak ratios of losartan and olmesartan were similar (0.68 and 0.69, respectively) and higher than those for telmisartan (0.48) and valsartan (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 losartan experienced at least one
clinical adverse event. This compares with 32.0% (n = 48) of the olmesartan group, 44.8% (n = 65) of the telmisartan group and 35.6% (n = 52) of the valsartan 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 randomisation (losartan, n = 1; olmesartan, n = 1; telmisartan n = 2). In the opinion of the investigator, these events were not related to the study drugs.11

### DISCUSSION

The principal finding of this study is that treatment with losartan results in a significantly greater reduction of cuff DBP than treatment with starting doses of olmesartan, telmisartan and valsartan. The superior efficacy of losartan in reducing cuff DBP was evident 2 weeks after the initiation of treatment and was maintained for the duration of the trial.12

As with the change in DBP, the losartan induced reduction in SBP was rapid in onset. Patients treated with losartan experienced a mean reduction in cuff SBP of 13.0 mmHg after 2 weeks of treatment. Mean reductions achieved in the three comparison groups at 2, but not 4 weeks were significantly lower ranging from 8.9 mmHg (olmesartan) to 10.8 mmHg (valsartan). The efficacy of losartan was maintained at 4 and 8 weeks (reductions of 13.4 and 11.3 mmHg, respectively), although the comparisons with olmesartan, telmisartan and valsartan did not achieve statistical significance at these time periods.13

The greater efficacy of losartan in reducing trough cuff DBP may be related to its relatively long half-life (12 - 18 hours).14

### Blood Pressure Differences and Outcome

Available data suggest that the small differences in DBP reduction between losartan and the other drugs in this study (approximately 2 - 4 mmHg) 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 5 mmHg 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 80 mmHg than in the group with a target DBP of 90 mmHg, although the actual difference in mean DBP achieved by these two groups was only 4.1 mmHg. 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.15

Several 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 - 159 mmHg were at 50% - 75% greater risk of cardiovascular disease than men with SBP of 120 - 139 mmHg. 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 10 mmHg 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.16

### Trough-to-Peak Ratio

The trough-to-peak ratio is a measure of the consistency of the antihypertensive 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.17 An optimal antihypertensive formulation should provide 24-hour efficacy

### Table IV. Adverse Events During the Active Treatment Period

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Losartan</th>
<th>Olmesartan</th>
<th>Telmisartan</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza-like Symptoms</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
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</tr>
<tr>
<td>Myalgia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>Toothache</td>
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<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Peripheral Oedema</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Migraine</td>
<td>0 (0.0)</td>
<td>3 (2.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
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. The total adverse event rate (which ranged from 31% for losartan to 45% for telmisartan) is similar. 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 Losartan. 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.

Endothelial Function and Angiotensin-II Blockade
Farhy and Colleagues demonstrated that losartan, olmesartan, telmisartan and valsartan reduced neointimal proliferation in a rat balloon.

CONCLUSION
This study has shown that the reduction in cuff DBP resulting from 8 weeks of treatment with losartan is greater than that seen following treatment with olmesartan, telmisartan or valsartan. Losartan also produced a reduction in cuff SBP that was greater than olmesartan, telmisartan and valsartan. 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.

REFERENCES