Comparative Effects of Ramipril on Ambulatory and Office Blood Pressures
A HOPE Substudy

Per Svensson, Ulf de Faire, Peter Sleight, Salim Yusuf, Jan Östergren

Abstract—In the HOPE-trial, the ACE inhibitor ramipril significantly reduced cardiovascular morbidity and mortality in patients at high risk for cardiovascular events. The benefit could only partly be attributed to the modest mean reduction of office blood pressure (OBP) during the study period (3/2 mm Hg). However, because according to the HOPE protocol ramipril was given once daily at bedtime and blood pressure was measured during the day, the 24-hour reduction of blood pressure may be underestimated based on OBP. Thirty-eight patients with peripheral arterial disease enrolled in the HOPE study underwent 24-hour ambulatory blood pressure (ABP) measurement before randomization and after 1 year. OBP was measured in the sitting position immediately before fitting the ABP measuring equipment to the patients. Ramipril did not significantly reduce OBP (8/2 mm Hg, P/NS) or day ABP (6/2 mm Hg, P=NS) after 1 year. Twenty-four–hour ABP was significantly reduced (10/4 mm Hg, P=0.03), mainly because of a more pronounced blood pressure lowering effect during nighttime (17/8 mm Hg, P<0.001). The night/day ratio was also significantly lowered in the ramipril group. ABP shows greater falls, especially at night, than OBP during treatment with ramipril given once daily at bedtime. Although, OBP is the correct comparator when comparing with previous large intervention trials and epidemiological studies, the effects on cardiovascular morbidity and mortality seen with ramipril in the HOPE study may, to a larger extent than previously ascribed, relate to effects on blood pressure patterns over the 24-hour period. (Hypertension. 2001;38:e28-e32.)

Key Words: antihypertensive therapy ■ blood pressure monitoring ■ ambulatory ■ clinical trials ■ peripheral vascular diseases ■ angiotensin-converting enzyme inhibitors ■ ramipril

In the recently published Heart Outcomes Prevention Evaluation (HOPE) study, treatment with the ACE inhibitor ramipril reduced cardiovascular mortality and morbidity in a broad range of patients at high risk for cardiovascular events.1 Patients included in the trial were >55 years of age and had a history of coronary artery disease, cerebrovascular disease, peripheral arterial disease, or diabetes mellitus with at least 1 additional cardiovascular risk factor. Approximately 50% of the patients were treated hypertensives.

Because the mean reduction of office blood pressure (OBP) with treatment was small (3/2 mm Hg) and the majority of patients already had well-controlled blood pressure at baseline (139/79 mm Hg),1 the benefit has been attributed mainly to other mechanisms of ACE inhibition than to blood pressure reduction per se. Such mechanisms could include beneficial effects on the endothelium or anti-atherosclerotic effects.2

According to the HOPE study protocol, 10 mg of ramipril was administered once daily before bedtime. OBP was measured at the study visits—which took place during the day and thus, in most instances, ~10 to 18 hours after drug intake; therefore, an underestimation of the 24-hour blood pressure reduction may be present when the evaluation is based on OBP measurements. In addition, a lowering effect on night and morning blood pressure may be of special importance, considering that cardiovascular events are most frequent during this time period.3,4

To assess the effect of ramipril on 24-hour blood pressure, 38 patients with peripheral vascular disease included in the HOPE study were subjected to ambulatory blood pressure (ABP) measurement for 24 hours at baseline before randomization and after 1 year on randomized treatment.

Methods

Patients
Patients included in the HOPE study with a history of intermittent claudication and an ankle-to–brachial systolic pressure index (ABI) <0.9 by Doppler ultrasonography at rest were recruited from study sites in Northern Stockholm (Karolinska and Danderyd Hospitals). Patients with rest pain, significant renal disease (serum creatinine...
>200 \( \mu \text{mol/L} \), uncontrolled hypertension, or heart failure with a known ejection fraction <40% were excluded.

Thirty-eight patients (19 men) with a mean age of 71 years were included after giving informed consent. Characteristics of the study patients are shown in Table 1. Twenty patients were randomized to receive ramipril; 18 patients, to receive placebo. The mean dosage of ramipril after 1 year was 8.1 mg. In 2 patients, ramipril was discontinued before 1 year because of cough. Other medications at baseline and after 1 year are shown in Table 2. In the ramipril group, 2 patients were treated with new or increased dosages of antihypertensive medications, and in 2 patients, antihypertensive medication was discontinued before 1 year because of cough. Other medications at baseline and after 1 year were available in all subjects, with a median of 94 readings per patient.

Adequate recordings with >80% of data retrieved were available in all subjects, with a median of 94 readings per patient (range, 78 to 98). Blood pressure was measured in the dominant arm in 5 cases. OBP at baseline was 152±21/83±7 mm Hg and 149±19/79±12 mm Hg (P=NS) in the ramipril and placebo groups, respectively, and 24-hour ABP at baseline was 148±19/78±9 mm Hg and 153±18/80±8 mm Hg (P=NS), respectively. The differences between baseline and 1 year are shown in Table 3 and Figure 1.

After 1 year, there were no significant differences in reduction in OBP (8/2 mm Hg, \( P=\text{NS} \)) or day ABP (6/2 mm Hg, \( P=\text{NS} \)) between the ramipril and placebo groups. Twenty-hour ABP was significantly reduced by ramipril compared with placebo (10/4 mm Hg, \( P=0.03 \)). A marked reduction by ramipril treatment was seen during nighttime (17/8 mm Hg, \( P<0.001 \)). At baseline, the night/day ratio of mean arterial pressure (MAP) averaged 0.86±0.06 in the ramipril group and 0.87±0.07 (P=NS) in the placebo group. After 1 year, the night/day ratio of MAP decreased in the ramipril group (0.82±0.06) compared with the placebo group (0.89±0.07, \( P<0.01 \)) (Figures 2 and 3).

**Discussion**

In this HOPE substudy, night ABP, 1 year after randomization, was significantly lowered during treatment with ramipril 10 mg once daily at bedtime compared with placebo. OBP and mean day ABP showed a modest and insignificant fall, which was of the same order as the significant but modest blood pressure fall observed in the overall HOPE study population. The failure to achieve statistical significance during daytime might well be due to the small numbers in this substudy. Because of the marked effect on night blood pressure by ramipril the night/day ratio decreased in the ramipril group compared with placebo (\( P<0.01 \)).

The pronounced blood pressure–lowering effect during nighttime may be explained by the fact that ramipril was given at bedtime. Ramipril has been reported to have a rather smooth effect on 24-hour blood pressure and can therefore be

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**TABLE 1. Main Characteristics of the Study Population (n=38)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ramipril (n=20)</th>
<th>Placebo (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70±6</td>
<td>72±8</td>
</tr>
<tr>
<td>Male/female</td>
<td>9/11</td>
<td>10/8</td>
</tr>
<tr>
<td>Smokers, current/former/never</td>
<td>4/14/2</td>
<td>4/11/3</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24±3</td>
<td>25±5</td>
</tr>
<tr>
<td>Ankle brachial index</td>
<td>0.62±0.13</td>
<td>0.53±0.14 p&lt;0.05</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or n.

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**TABLE 2. Pharmacological Therapy in Patients Randomized to Treatment with Ramipril or Placebo at Baseline and After 1 Year**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Baseline</th>
<th>One Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ramipril (n=20)</td>
<td>Placebo (n=18)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Diuretics</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aspirin</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Nitrates</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Values are expressed as n.
taken once daily for treatment of hypertension. As with all antihypertensive agents, however, there is a variation of the blood pressure effect during 24 hours, with a peak effect of ramipril 3 to 6 hours after administration. The peak/trough ratio of ramipril administered once daily is about 0.5, ie, =50% of the maximum effect is still present after 24 hours. 7, 8 OBP in this substudy (and, most likely, in the HOPE patients overall) was measured 12 hours after administration of ramipril.

The usual finding in antihypertensive studies is a more pronounced effect of treatment on OBP than on ABP. Another possible explanation for the difference between earlier results and our study may be that in hypertension trials, patients are generally selected on the basis of OBP, ie, patients in the upper part of the distribution of OBP in the population are included. At follow-up, regression to the mean will make the patients have a lower OBP that is more closely related to their “true” blood pressure (which also will correlate better to their ABP). Antihypertensive intervention in the upper part of the OBP distribution may therefore cause a relatively greater OBP reduction than ABP reduction (which is the usual finding when comparing OBP and ABP in intervention trials). In HOPE study and in our substudy, patients were not selected on the basis of having high OBP and may thus be regarded to represent a more “normal” OBP distribution. With antihypertensive intervention in this population, OBP reduction and ABP reduction will thus be more closely related.

The mean reduction of OBP that was achieved in HOPE overall throughout the study period (=3/2 mm Hg) would, compared with previous hypertension trials, explain a reduction of stroke incidence of 13% and a reduction of myocardial infarctions of 5%. In HOPE, however, the relative reductions of these endpoints were 31% and 20%, respectively. Therefore, it has been claimed that other vascular protective effects of ACE inhibition, besides blood pressure reduction per se, most probably contributed to the positive effects.

Based on our findings, it may be suggested that more of the benefits of ramipril in HOPE may be related to blood pressure reduction (especially during nighttime) than what was explained by the effects on OBP seen in both the main study and this study. However, the knowledge of blood pressure as a cardiovascular risk factor is mainly based on epidemiological and intervention trials in which blood pressure was recorded in the office. On the other hand, in several cohort studies, ABP has been shown to predict cardiovascular risk better than OBP.

Because previous trials are based on OBP, it is difficult to relate a reduction of ABP to a reduction of cardiovascular risk. There is a possibility that previous trials may have both under- (or over-) estimated effects based on OBP. Therefore, the correct comparator between the trials is OBP and not

### Table 3. OBP and ABP in Patients Randomized to Ramipril and Placebo at Baseline and Reduction of Blood Pressure at 1 Year

<table>
<thead>
<tr>
<th>Blood Pressures</th>
<th>Baseline</th>
<th></th>
<th></th>
<th>BP Reduction at Year One</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ramipril</td>
<td>Placebo</td>
<td>P</td>
<td>Ramipril</td>
<td>Placebo</td>
<td>P</td>
</tr>
<tr>
<td>Systolic OBP, mm Hg</td>
<td>152±21</td>
<td>149±19</td>
<td>NS</td>
<td>12±24</td>
<td>4±27</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic OBP, mm Hg</td>
<td>83±7</td>
<td>79±12</td>
<td>NS</td>
<td>5±10</td>
<td>3±12</td>
<td>NS</td>
</tr>
<tr>
<td>24-hour SBP (mm Hg)</td>
<td>148±19</td>
<td>153±18</td>
<td>NS</td>
<td>12±15</td>
<td>2±10</td>
<td>0.03</td>
</tr>
<tr>
<td>24-hour DBP (mm Hg)</td>
<td>78±9</td>
<td>80±8</td>
<td>NS</td>
<td>5±7</td>
<td>1±6</td>
<td>0.03</td>
</tr>
<tr>
<td>Day SBP (mm Hg)</td>
<td>153±20</td>
<td>158±19</td>
<td>NS</td>
<td>10±15</td>
<td>4±12</td>
<td>NS</td>
</tr>
<tr>
<td>Day DBP (mm Hg)</td>
<td>83±9</td>
<td>84±9</td>
<td>NS</td>
<td>4±7</td>
<td>2±7</td>
<td>NS</td>
</tr>
<tr>
<td>Night SBP (mm Hg)</td>
<td>136±20</td>
<td>142±19</td>
<td>NS</td>
<td>16±16</td>
<td>-1±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Night DBP (mm Hg)</td>
<td>69±9</td>
<td>71±9</td>
<td>NS</td>
<td>7±7</td>
<td>-1±6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD. SBP indicates systolic blood pressure; DBP, diastolic blood pressure.
P values denote differences between patients randomized to ramipril and placebo respectively.
ABP. To our knowledge, HOPE is the only large trial in which an antihypertensive agent, according to the study protocol, has been recommended to be given at bedtime and may be unique compared with other trials in regard to effects on day-night variation of blood pressure and on the timing of OBP measurement to drug intake.

In some epidemiological outcome studies, cardiovascular risk showed an inverse association with the degree of blood pressure reduction from day to night. In a substudy on 393 patients (1666 patient years) in the placebo arm of the SYST-Eur study, the night/day ratio of ABP, independently of 24-hour blood pressure levels, showed an inverse association to cardiovascular events during follow-up. For each 10% increment in night/day ratio, the cardiovascular risk increased 41%.

Interestingly, in our study the night/day ratio of blood pressure, at baseline averaging 0.86 in both groups, differed ~8% at the 1 year follow-up between placebo and ramipril groups (0.89 versus 0.82, respectively). Thus, the increment in night/day ratio in our study is coherent with the reduction of cardiovascular events seen in HOPE.

There has been concern that a lowering of night blood pressure from normal levels in patients with cardiovascular disease may be associated with negative effects due to cerebral and coronary hypoperfusion. If the findings of this substudy reflect effects on night blood pressure in the main HOPE population (with manifest cardiovascular disease and at average “normal” blood pressure), the clinical outcomes of HOPE with a risk reduction of stroke with 32% strongly suggests that this concern has been unwarranted.

Important differences between this small substudy and the HOPE overall population involve the principal inclusion

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**Figure 2.** Night/day ratio of ambulatory MAP in patients randomized to ramipril (A, n=20) and placebo (B, n=18) at baseline and 1 year.

**Figure 3.** Reduction of night-day ratio of ambulatory MAP at 1 year in patients randomized to placebo (n=18) and ramipril (n=20).
criteria (100% PVD versus 19% PVD), higher OBP at baseline (151/81 mm Hg versus 139/79 mm Hg), and older age (71 years versus 66 years). These differences may account for some of the findings of this study and make generalization of the findings to the entire HOPE study population uncertain.

However, the findings of this study suggest that the mode of blood pressure measurement and the timing of drug intake in relation to blood pressure measurement are important factors to consider when assessing blood pressure effects and relating these to clinical outcomes.

In conclusion, ABP showed greater falls, especially at night, than did OBP during treatment with ramipril given once daily at bedtime. However, OBP is the correct comparator to the previous large trials and most epidemiological studies. Although our data are based on a small and defined subset of HOPE patients, the effects on cardiovascular morbidity and mortality seen with ramipril in the HOPE study may to a larger extent than previously ascribed relate to effects on blood pressure patterns over the 24-hour period.

References
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