A Multicenter, 14-Week Study of Telmisartan and Ramipril in Patients With Mild-to-Moderate Hypertension Using Ambulatory Blood Pressure Monitoring

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Background: Blood pressure (BP) has a circadian pattern with a morning surge that is associated with an increased risk of acute coronary and cerebrovascular events. In a prospective, randomized, open-label, blinded-endpoint, parallel-group, multicenter, forced-titration study of telmisartan and ramipril, the efficacy of both drugs on mean ambulatory diastolic BP (DBP) and systolic BP (SBP) during the last 6 h of a 24-h dosing interval was evaluated.

Methods: After screening and a single-blind run-in phase, 812 adults with mild-to-moderate hypertension (defined as a mean seated DBP ≥95 mm Hg and ≤109 mm Hg and a 24-h ABPM mean DBP ≥85 mm Hg) were randomized to the open-label, 14-week, forced-titration, active-treatment phase as follows: telmisartan 40 mg/80 mg/80 mg (n = 405) or ramipril 2.5 mg/5 mg/10 mg (n = 407), once daily in the morning. The primary efficacy variable was change from baseline in the last 6-h mean DBP and SBP at 8 and 14 weeks as assessed by ambulatory BP monitoring (ABPM). Secondary efficacy variables were changes from baseline in BP control during each of the 24-h periods and in-clinic trough cuff BP.

Results: Telmisartan 80 mg was superior to ramipril 5 mg and 10 mg in change from baseline in the last 6-h ABPM mean DBP and SBP at both 8 and 14 weeks (both P < .0001), respectively. At 14 weeks, the adjusted mean change from baseline in DBP for telmisartan 80 mg was −8.8 mm Hg compared with that for ramipril 10 mg of −5.4 mm Hg (P < .0001). For SBP, the adjusted mean change from baseline for telmisartan 80 mg was −12.7 mm Hg compared with that for ramipril 10 mg of −7.9 mm Hg (P < .0001). At 14 weeks, telmisartan 80 mg also yielded superior reductions from baseline in trough cuff BP compared with ramipril 10 mg (DBP: −11.0 mm Hg v −7.8 mm Hg, respectively; SBP: −14.3 mm Hg v −9.1 mm Hg, respectively; both P < .0001). Measures of 24-h BP control favored telmisartan 80 mg versus ramipril 10 mg (P < .0001), as did other secondary ABPM endpoints during the daytime, night-time, and morning periods. Treatment-related adverse events were uncommon; patients treated with ramipril had a higher incidence of cough than those treated with telmisartan (10.1% v 1.5%, respectively).

Conclusions: Telmisartan 80 mg was consistently more effective than ramipril 10 mg in reducing both DBP and SBP during the last 6 h of the dosing interval, a measure of the early morning period when patients are at greatest risk of life-threatening cardiovascular and cerebrovascular events. Telmisartan 80 mg was also more effective than ramipril 10 mg in reducing BP throughout the entire 24-h dosing interval. Both drugs were well tolerated. Am J Hypertens 2006;19:104–112 © 2006 American Journal of Hypertension, Ltd.

Key Words: Ambulatory blood pressure, monitoring, clinical trial, hypertension, telmisartan, ramipril.
Hypertension is an established risk factor for myocardial infarction, sudden death, congestive heart failure, stroke, and end-stage renal disease. Even when blood pressure (BP) control as assessed in the office setting meets established target values, many patients who appear to be treated adequately remain at increased risk for cardiovascular events and end-stage renal disease. Cross-sectional and longitudinal studies have supported the hypothesis that adverse outcomes are directly related to the inability to maintain 24-h average BP within the normal range.

Both angiotensin receptor blockers (ARB) and angiotensin-converting enzyme (ACE) inhibitors are safe and effective interventions for patients with hypertension. With appropriate pharmacokinetics and sustained receptor occupancy, agents that inhibit the activity of the renin–angiotensin–aldosterone system (RAAS) can provide effective BP control with once-daily dosing.

This prospective, randomized, open-label, blinded-endpoint (PROBE) trial was designed to compare the efficacy of once-daily telmisartan 80 mg with ramipril 5 mg and 10 mg in adult patients with mild-to-moderate hypertension. Both the ARB and the ACE inhibitor are long-acting antihypertensive medications documented to be effective in patients with mild-to-moderate hypertension. To assess the comparative efficacy of the two drugs on BP control, ambulatory BP monitoring (ABPM) was used for continuous monitoring of efficacy. Because the last 6 h of the 24-h dosing interval may constitute a time of increased cardiovascular risk, this study focused on the effects of both drugs during this period while also assessing overall BP control.

**Methods**

**Study Design**

The study was a 14-week (active treatment) PROBE, parallel-group, forced-titration trial designed to evaluate the safety and efficacy, as measured by ABPM, of telmisartan (80 mg) and ramipril (5 mg and 10 mg) in adult men and women with mild-to-moderate hypertension. This international study was conducted at 81 US and Canadian centers between October 1, 2002, and July 17, 2003. The protocol and informed consent were reviewed and approved by a duly constituted institutional review board or ethics committee for each study site; some sites used a centralized institutional review board contracted for the study. The trial was carried out in accordance with the principles of the 1996 Declaration of Helsinki, the International Committee on Harmonisation (ICH) Harmonized Tripartite Guideline for Good Clinical Practice, and applicable regulatory requirements. Each patient was required to provide written informed consent.

Eligibility Criteria

To be eligible, patients ≥18 years of age were required to have mild-to-moderate hypertension at baseline as defined by a mean seated diastolic BP (DBP) ≥95 mm Hg and ≤109 mm Hg measured by manual cuff sphygmomanometer and a 24-h mean DBP ≥85 mm Hg measured by ABPM using SpaceLabs 90207 monitors (SpaceLabs, Redmond, WA) during the morning (6:00 AM to 11:59 AM), daytime (6:00 AM to 9:59 PM), and night-time (10:00 PM to 5:59 AM) periods.

Patients were excluded if they were found to have a mean seated systolic BP (SBP) ≥180 mm Hg or a mean seated DBP ≥110 mm Hg during any visit of the placebo run-in or if they had secondary hypertension, congestive heart failure, stroke within 6 months of study entry, percutaneous transluminal coronary angioplasty within 3 months of study entry, hemodynamically significant valvular or myocardial obstructive pathologic conditions, or clinically relevant arrhythmias. Night-shift workers who routinely slept during the day and worked from midnight to 4 AM were excluded. Patients were also excluded for relevant organ system disease(s), such as poorly controlled diabetes mellitus, significant hepatic, or renal dysfunction, or any serious clinical condition. Medication-related exclusions covered known hypersensitivity to any component of the study drugs, angioedema during treatment with an ACE inhibitor or an ARB, the need for concurrent medications that might affect BP control, history of noncompliance with prescribed medications, and substance abuse within the previous 6 months. Laboratory findings that might lead to exclusion from the study were significant sodium depletion, hypokalemia, or hyperkalemia; evidence of uncorrected volume depletion; hereditary fructose intolerance; and biliary tract obstruction. Adult women were not allowed to participate if they were breastfeeding or of childbearing potential and at risk for becoming pregnant.

**Study Protocol**

The study was divided into three phases: 1) screening (1 to 7 days); 2) single-blind (placebo) run-in phase (2 to 4 weeks); and 3) active treatment (open-label) phase (14 weeks) (Fig. 1). During the screening phase, patients were evaluated to ensure that they met all inclusion criteria, with no reason for exclusion, and were weaned off any current antihypertensive medications. Patients previously treated with an ACE inhibitor, ARB, or diuretic underwent a 4-week run-in period, and all other enrollees underwent a 2-week run-in period. At the end of the single-blind run-in phase, baseline cuff clinic and ambulatory BP were measured, and qualifying patients were randomized to treatment with telmisartan 40 mg or ramipril 2.5 mg once daily, at approximately the same time each morning. Clinic visits were to be scheduled in the morning between 7 AM and 10 AM, no later than 24 h after the last dose of trial medication.
After 2 weeks, seated cuff BP was measured and the telmisartan and ramipril doses were up-titrated to 80 mg and 5 mg, respectively. Six weeks later, seated cuff BP was measured and ABPM was performed followed by the second “forced” titration. At this time, patients randomized to ramipril were up-titrated to 10 mg daily; although participating in the mechanics of the up-titration process, telmisartan-treated patients remained on the 80-mg dose. Patients then continued on the highest dose of their respective study medication for the remaining 6 weeks of the active treatment phase, at the end of which seated cuff BP was measured and the final ABPM was performed.

All administrative procedures and medical evaluations, including a laboratory evaluation, were performed during the screening period. At each scheduled visit throughout the study, seated cuff BP and compliance with study medication were monitored, and adverse events or use of concomitant therapy were recorded. Urine pregnancy testing was performed as appropriate before randomization and at the end of the study visit.

Study Endpoints

The primary efficacy endpoints were the changes from baseline in the last 6-h mean (relative to dosing time) DBP and SBP as measured by ABPM at the end of both the 8-week (telmisartan 80 mg/day v ramipril 5 mg/day) and 14-week (telmisartan 80 mg/day v ramipril 10 mg/day) treatment periods.

Secondary efficacy endpoints measured at the end of both the 8-week and 14-week treatment periods were also evaluated. Secondary ABPM endpoints included changes from baseline in the following parameters: 24-h ABPM mean (relative to dosing time) for DBP and SBP; ABPM mean (relative to clock time) for DBP and SBP during the morning (6:00 AM to 11:59 AM), daytime (6:00 AM to 9:59 PM), and night-time (10:00 PM to 5:59 AM) periods. Blood pressure response based on the 24-h ABPM mean BP measurements were also determined: DBP response was defined as 24-h ABPM mean DBP <80 mm Hg or a change from baseline of ≥10 mm Hg; and SBP response was defined as 24-h ABPM mean SBP <130 mm Hg or a change from baseline of ≥10 mm Hg. Secondary endpoints related to the manual cuff BP measurements included the changes from baseline in the mean seated trough DBP and SBP and BP response. The DBP response was defined as mean seated cuff DBP <90 mm Hg at trough or a change from baseline of ≥10 mm Hg. The SBP response was defined as mean seated SBP <140 mm Hg at trough or a change from baseline of ≥10 mm Hg. Safety was assessed by evaluation of adverse events as well as by BP and pulse rate measurements taken at each visit of the study.

Statistical Methods

The primary evaluation compared treatment effects using an analysis of covariance including treatment and center as main effects and the last 6-h ABPM mean at baseline as a covariate. Testing of the multiple primary endpoints, as well as the multiple hypotheses (ie, noninferiority and superiority), were prespecified to be performed in a hierarchical order with conclusions drawn on subsequent testing only if previous tests were found to be significant. As such, all testing of the hierarchical closed-testing procedure was performed at a significance level of \( \alpha = 0.05 \).

In evaluating the noninferiority of telmisartan compared with ramipril, the per-protocol analysis set for the respective comparison after 8 or 14 weeks of treatment was used. The 95% confidence interval (CI) for the least-square mean difference between treatments (telmisartan minus ramipril) was calculated using the mean squared error (MSE) from the analysis. If the upper limit of the 95% CI for the mean difference between treatments was <0, superiority was concluded and any other subsequent testing in the closed-testing procedure was carried out.

All secondary endpoints were assessed using the respective full analysis set using \( \alpha = 0.05 \). In the case of a patient discontinuing the study prematurely, last observation carried forward principles were followed in determining the full analysis sets related to in-clinic trough cuff endpoints. For secondary endpoints of changes from baseline, the analysis described for the primary endpoints was performed. Responder rates were evaluated using Mantel-Haenszel statistics adjusted for center.

Results

Study Patients

During the course of the trial, 1998 patients were screened, 812 of whom were randomized. The primary reasons for the 1186 patients who failed to be randomized were that the patients did not meet either the required cuff measurements of seated DBP ≥95 mm Hg and ≤109 mm Hg and
24-h mean ≥85 mm Hg as required by the protocol. However, most patients failed because of the strict criterion of 24-h mean DBP ≥85 mm Hg. A total of 90 (11.1%) of the randomized patients who received study medication were prematurely discontinued from the trial. Discontinuations occurred in approximately equal numbers from both arms: 44 of 405 (10.9%) from the telmisartan group and 46 of 407 (11.3%) from the ramipril group. Reasons for patient discontinuation after randomization are listed in Fig. 2. Discontinuations in the ramipril group were predominantly caused by adverse events (n = 23; 5.7%). The subjects were predominantly middle-aged white men with a history of approximately 7 years of hypertension. There were no significant differences in baseline ambulatory or clinic BP in these truly hypertensive patients or in mean body mass index (Table 1).

**Ambulatory BP**

The mean ambulatory BP obtained at baseline and after 8 and 14 weeks of treatment during the different periods of the 24-h interval are summarized in Table 2. After 8

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**Table 1. Baseline characteristics of patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Telmisartan 40 mg/80 mg/80 mg</th>
<th>Ramipril 2.5 mg/5 mg/10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>405</td>
<td>407</td>
</tr>
<tr>
<td>Male (%)</td>
<td>65.2</td>
<td>68.6</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>52.7 (10.1)</td>
<td>52.5 (9.5)</td>
</tr>
<tr>
<td>White (%)</td>
<td>87.2</td>
<td>88.2</td>
</tr>
<tr>
<td>Mean (SD) body mass index (kg/m²)</td>
<td>30.52 (5.22)</td>
<td>30.83 (5.53)</td>
</tr>
<tr>
<td>Mean duration of hypertension (y)</td>
<td>6.9</td>
<td>7.6</td>
</tr>
<tr>
<td>Mean (SD) 24-h SBP*</td>
<td>148.2 (11.6)</td>
<td>147.6 (11.8)</td>
</tr>
<tr>
<td>Mean (SD) 24-h DBP*</td>
<td>92.5 (6.3)</td>
<td>92.5 (5.9)</td>
</tr>
<tr>
<td>Mean (SD) trough cuff clinic SBP*</td>
<td>153.9 (12.2)</td>
<td>152.5 (12.8)</td>
</tr>
<tr>
<td>Mean (SD) trough cuff clinic DBP*</td>
<td>99.7 (4.2)</td>
<td>99.8 (4.3)</td>
</tr>
</tbody>
</table>

There were no significant differences in baseline ambulatory or clinic BP in these truly hypertensive patients as well as in mean body mass index. DBP – diastolic blood pressure; SBP – systolic blood pressure.

* Baseline measurements for patients previously treated with an ACE inhibitor, ARB, or diuretic were taken after the 4-week run-in period.

For all other patients, baseline measurements were taken after the 2-week run-in period.
(telmisartan 80 mg v ramipril 5 mg) and 14 (telmisartan 80 mg v ramipril 10 mg) weeks of active treatment, patients treated with telmisartan demonstrated significantly greater ($P < .0001$) decreases in ambulatory systolic BP and diastolic BP during each period of the 24-h administration interval. When analyzing the primary efficacy endpoints, telmisartan 80 mg demonstrated superiority to ramipril 10 mg in the reduction from baseline of both DBP and SBP during the last 24 h of the dosing interval. At 14 weeks, the adjusted mean change from baseline in the last 6-h ABPM mean DBP for telmisartan 80 mg (−8.8 mm Hg) was significantly greater than that for ramipril 10 mg (−5.4 mm Hg; $P < .0001$). For SBP, the adjusted mean change from baseline in the last 6-h ABPM mean was also significantly greater for telmisartan 80 mg (−12.7 mm Hg) compared with ramipril 10 mg (−7.9 mm Hg; $P < .0001$). Telmisartan 80 mg also demonstrated superiority to ramipril 5 mg in the reduction of both of these primary endpoints. At 8 weeks, the adjusted mean change from baseline in the last 6-h ABPM mean DBP for telmisartan 80 mg (−7.8 mm Hg) was significantly greater than for ramipril 5 mg (−4.1 mm Hg; $P < .0001$), with an adjusted mean difference of −3.6 in favor of telmisartan 80 mg. For SBP, the adjusted mean change from baseline in the last 6-h ABPM mean was also significantly greater for telmisartan 80 mg (−11.1 mm Hg) compared with ramipril 5 mg (−5.6 mm Hg; $P < .0001$), with an adjusted mean difference of −5.5 in favor of telmisartan 80 mg. Moreover, as illustrated in Fig. 3, the 24-h profile of the reductions in both DBP and SBP hourly means for telmisartan 80 mg were consistently greater than those for ramipril 10 mg (at the end of 14 weeks of treatment). Similar 24-h profile of the reductions in both DBP and SBP hourly means were observed at the end of 8 weeks of treatment comparing telmisartan 80 mg and ramipril 5 mg.

For each of the three variables categorizing BP response based on the 24-h ABPM means, significantly higher response rates were found for telmisartan 80 mg ($P < .01$) compared with ramipril 10 mg. At 14 weeks, the following response rates were recorded for telmisartan 80 mg: DBP response (53.5%), and SBP response (70.4%) versus ramipril 10 mg (34.3%, and 61.0%, respectively). Similar differences were also found when comparing telmisartan 80 to ramipril 5 mg at the end of 8 weeks of treatment.

### Clinic BP

Significant BP reductions were observed in both groups during treatment (Table 3). Results of analyses comparing the changes from baseline in the in-clinic trough cuff BP also confirmed those of the primary endpoints. The adjusted mean changes from baseline at the end of 14 weeks of treatment significantly favored telmisartan 80 mg (DBP/SBP: −11.0/−14.3 mm Hg) compared with ramipril 10 mg (DBP/SBP: −7.8/−9.1 mm Hg; both $P < .0001$). Significant differences in favor of telmisartan 80 mg versus ramipril 5 mg were also observed at the end of 8 weeks of treatment (telmisartan 80 mg DBP/SBP: −10.3/−13.7 mm Hg versus ramipril 5 mg DBP/SBP: −6.5/−7.4 mm Hg; both $P < .0001$). Significantly higher response rates based on in-clinic trough cuff response rates were found for telmisartan ($P < .01$) compared with ramipril 10 mg. At 14 weeks, the following response rates were recorded for telmisartan 80 mg; DBP response (60.5%) and SBP response (70.7%) versus ramipril 10 mg (46.8% and 62.7%, respectively). Similar differences were also found when comparing telmisartan 80 mg to ramipril 5 mg at the end of 8 weeks of treatment.

### Tolerability and Safety

Both drugs were well tolerated and adverse events were consistent with the known adverse event profiles. The majority of adverse events were of mild-to-moderate severity. Only four drug-related adverse events occurred at a

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### Table 2. Antihypertensive effects of telmisartan 80 mg and ramipril 5 mg or 10 mg on mean systolic/diastolic ambulatory blood pressure (mm Hg) at week 8 and week 14 compared with baseline

<table>
<thead>
<tr>
<th>Variable/Drug</th>
<th>Baseline Mean</th>
<th>Week 8</th>
<th>Week 14</th>
<th>$P$ Value v Ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean last 6-h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telmisartan</td>
<td>142.2/88.6</td>
<td>131.1/80.9</td>
<td>129.5/79.8</td>
<td>&lt;.0000</td>
</tr>
<tr>
<td>Ramipril</td>
<td>141.9/89.2</td>
<td>136.3/85.1</td>
<td>134.0/83.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean 24-h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telmisartan</td>
<td>148.2/92.5</td>
<td>135.3/83.6</td>
<td>133.4/82.6</td>
<td>&lt;.0000</td>
</tr>
<tr>
<td>Ramipril</td>
<td>147.6/92.5</td>
<td>138.9/87.0</td>
<td>136.9/85.8</td>
<td>&lt;.0000</td>
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<tr>
<td>Mean morning</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Telmisartan</td>
<td>152.8/97.2</td>
<td>140.1/88.5</td>
<td>138.5/87.5</td>
<td>&lt;.0000</td>
</tr>
<tr>
<td>Ramipril</td>
<td>152.3/97.4</td>
<td>144.6/92.6</td>
<td>143.0/91.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean daytime</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telmisartan</td>
<td>153.3/96.8</td>
<td>139.9/87.7</td>
<td>138.3/86.7</td>
<td>&lt;.0000</td>
</tr>
<tr>
<td>Ramipril</td>
<td>152.7/96.9</td>
<td>143.0/90.7</td>
<td>141.5/89.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean night-time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telmisartan</td>
<td>137.8/83.6</td>
<td>126.1/75.4</td>
<td>124.7/74.7</td>
<td>&lt;.0000</td>
</tr>
<tr>
<td>Ramipril</td>
<td>137.1/83.9</td>
<td>130.8/79.5</td>
<td>127.9/77.7</td>
<td>&lt;.0000</td>
</tr>
</tbody>
</table>
rate of at least 1% in either treatment arm: peripheral edema (telmisartan, 4 [1.0%]; ramipril, 0 [0.0%]), dizziness (telmisartan, 6 [1.5%]; ramipril, 4 [1.0%]), headache (telmisartan, 4 [1.0%]; ramipril, 6 [1.5%]), and cough (telmisartan, 1 [0.2%]; ramipril, 33 [8.1%]). Severe adverse events were reported by 45 patients during the active treatment phase of the trial: two (0.5%) by patients treated with telmisartan 40 mg, 13 (3.3%) with telmisartan 80 mg.
mg. 10 (2.5%) with ramipril 2.5 mg, 12 (3.0%) with ramipril 5 mg, and 8 (2.1%) with ramipril 10 mg. Fourteen patients reported a serious adverse event. None of the serious adverse events were considered to be drug-related.

Discussion

The present study demonstrated that telmisartan was consistently significantly more effective than ramipril in controlling BP during the last 6 h of the dosing interval—a time that correlates with the early morning period during which there is the greatest risk of cardiovascular and cerebrovascular events. In addition, telmisartan was consistently significantly more effective than ramipril in controlling BP throughout the entire 24-h dosing interval. The consistently greater reductions in both DBP and SBP with telmisartan 80 mg, compared with ramipril 5 mg and 10 mg, throughout the entire 24-h dosing interval are not only statistically significant but clinically significant as well. The superiority of telmisartan is further confirmed by the significantly greater reductions in manual cuff BP. Moreover, ambulatory and clinic systolic and diastolic BP response rate were significantly greater with telmisartan. These results may be surprising but they are in agreement with those of a recent study showing that the BP-lowering effect of ramipril was statistically less than that of telmisartan. In fact, comparison with baseline showed that ambulatory BP reduction with ramipril was mostly restricted to its peak effect.19

Previous studies have found that telmisartan is superior to other widely used angiotensin receptor blockers such as losartan and valsartan at the end of the dosing interval.20,21 In addition, White et al7 showed that after a missed dose, telmisartan had a large effect on systolic BP at the end of the dosing period as compared with valsartan. Taken together, these studies do suggest that the pharmacology of the angiotensin II receptor blocker telmisartan, whether associated with a tissue-base half-life difference or a plasma half-life difference, or both, plays an important role in the pharmacologic effects of this agent during the latter portion of the dosing interval.

Because patients receiving once-daily pharmacotherapy usually take these drugs in the morning, the nadir in blood levels of antihypertensive medication(s) occurs just at the time that patients are at highest risk for potential circadian variation–related acute events. Indeed, good evidence suggests that the early morning is a period of increased cardiovascular risk. Muller et al analyzed the time of day of sudden cardiac death reported on death certificates of patients dying outside of a hospital.10 In their analysis of 2203 cases from Massachusetts, they report that the incidence of sudden cardiac deaths increased sharply between 7 AM and 11 AM. In subjects in the Thrombolysis in Myocardial Infarction Phase II (TIMI II) trial, 34% of all myocardial infarctions occurred between 6 AM and noon.11 The administration of α-blocking agents in the preceding 24 h was found to lower the incidence of morning infarctions, suggesting that the antihypertensive action of the α-adrenergic blocker may be contributory.11,12 The morning surge in BP may also be related to the incidence of silent and clinically acute cerebrovascular events.13 In support of this hypothesis, Kario et al report that higher morning acceleration in BP is a significant independent risk factor for stroke in older patients with hypertension.14 The potential importance of protection against the morning surge in BP may have been reflected in the results of the Heart Outcomes Prevention Evaluation (HOPE) study, the only large BP outcome trial in which the study protocol recommended that the ACE inhibitor be given at bedtime. Thus, despite a lack of efficacy for most of the next day, the beneficial effect of ramipril on outcomes may be at least partially attributed to the action of the drug in the early morning, for this study a time approximately 8 to 12 h after administration.15–18 The relationship between BP reduction and cardiovascular events is continuous and independent of other risk factors.2 Data from a number of

| Table 3. | Antihypertensive effects of telmisartan 80 mg and ramipril 5 mg or 10 mg on clinical blood pressure (mm Hg) |
|---|---|---|
| **Variable** | **Telmisartan** | **Ramipril** | **P Value v Ramipril** |
| **Baseline** | | | |
| Systolic BP | 153.9 | 152.5 | NS |
| Diastolic BP | 99.7 | 99.8 | NS |
| **Week 8** | | | |
| Systolic BP | 140.2 | 145.1 | <.0000 |
| Diastolic BP | 89.4 | 93.3 | <.0001 |
| Change from baseline (systolic/diastolic) | −13.7/10.3 | −7.4/6.5 | <.0001 |
| **Week 14** | | | |
| Systolic BP | 139.6 | 143.4 | <.0000 |
| Diastolic BP | 88.7 | 92.0 | <.0001 |
| Change from baseline (systolic/diastolic) | −14.3/11.0 | −9.1/7.8 | <.0001 |

BP = blood pressure; NS = not significant.
observational and randomized controlled trials indicate that small decreases in BP can significantly decrease cardiovascular events. For example, Cook et al report that a 2-mm Hg reduction in DBP would be anticipated to decrease the risk of CHD by 6% as well as to lower the risk of stroke and transient ischemic attacks by 15%. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, high-risk cardiovascular patients whose BP was controlled had a lower incidence of coronary heart disease endpoints compared with those whose BP was not controlled. Thus the superior BP control afforded by telmisartan has the potential to reduce the risks associated with hypertension. Indeed because telmisartan provides stable drug levels throughout the 24-h dosing interval, it has the potential to prevent acute cardiovascular events that may be related to circadian fluctuations in BP. It is noteworthy that the potential of telmisartan for cardiovascular and cerebrovascular protection is currently being explored in two randomized, double-blind, multicenter outcome studies.

References


Appendix

The PRISMA II Investigators are as follows:

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Timothy Lindamood
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Brian Craig
Jeffrey Daiter
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Yves Lacourcière
Daniel Landry
Jacques Lenis
Patrick Ma
Elias Maraghi
Dennis O’Keefe
Osvaldo Papini
Rob Petrella
Joel Poulion
Calvin Powell
Brian Ramjattan
Don Rhodes
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