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The Effect Duration of Candesartan Cilexetil Once Daily, in Comparison with Enalapril Once Daily, in Patients with Mild to Moderate Hypertension

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Objective: To determine the antihypertensive efficacy, effect duration and safety of the angiotensin II type1 receptor blocker candesartan cilexetil and the angiotensin converting enzyme inhibitor enalapril once daily in patients with mild to moderate hypertension.

Methods: A multicenter, randomised, double-blind parallel group study was performed in Finland, France, the Netherlands, Spain and Sweden. Three-hundred-and-ninety-five men and women in the age range 20–80 years with primary hypertension were randomised to an 8-week double-blind treatment period with either candesartan cilexetil 8–16 mg or enalapril 10–20 mg once daily, with forced dose titration after 4 weeks. Non-invasive ambulatory blood pressure was measured for 36 h at baseline and after 8 weeks. The primary efficacy variable was the change in mean diastolic and systolic ambulatory blood pressure 22–24 h post-dose.

Results: There was a significant difference in the adjusted mean difference for the change from baseline to week 8 between candesartan cilexetil and enalapril 22–24 h post-dose by −3.5 mmHg (95% confidence interval, CI: −6.8 to −0.3 mmHg; p < 0.032) in ambulatory systolic blood pressure and −3.0 mmHg (95% CI: −5.1 to −0.8 mmHg; p < 0.008) in ambulatory diastolic blood pressure. There was a significant difference in adjusted mean daytime ambulatory blood pressure 24–36 h post-dose by −4.2 mmHg (95% CI: −6.8 to −1.6 mmHg; p < 0.002)/−3.5 mmHg (95% CI: −5.1 to −1.8 mmHg; p < 0.001). Both drugs were generally well tolerated.

Conclusion: The results of the present study suggest that advantages may be attributed to the use of candesartan cilexetil, as compared to enalapril in the treatment of patients with essential hypertension. In comparison with enalapril 20 mg, candesartan cilexetil 16 mg more effectively lowered blood pressure at trough and in particular on the day following the day after the last dose. Key words: ACE inhibitor, angiotensin receptor blocker, antihypertensive, candesartan cilexetil, enalapril, hypertension.

INTRODUCTION

Blood pressure levels have been shown to be positively and continuously related to the risks of stroke, major coronary heart disease events, heart failure and renal disease [1,2]. The renin–angiotensin system plays an important role in the regulation of blood pressure as well as electrolyte and fluid homeostasis [3,4]. Compelling evidence also suggest that activation of the renin–angiotensin system is associated with a disordered cardiovascular risk profile as well as cardiovascular disease [5,6]. Following successful research in drug development during the last decades it has been made possible effectively to block the renin–angiotensin system at several steps by orally active inhibitors [7,8]. The angiotensin-converting enzyme (ACE) inhibitors and the specific angiotensin II receptor blockers are two of the six main drug classes used worldwide for blood pressure lowering treatment [2].

Lowering of high blood pressure has been shown to reduce the incidence of cardiovascular events, such as stroke and coronary heart disease [9,10]. Recent randomised controlled trials have demonstrated that an ACE inhibitor-based treatment is as effective as conventional therapy with thiazides or beta-blockers in reducing the total number of cardiovascular events [11–13]. Some specific advantages have been observed in relation to the blockade of the renin–angiotensin system. In patients with uncomplicated hypertension, ACE inhibitor treatment was associated with fewer new cases of diabetes mellitus [12]. Moreover, patients with diabetes more often remained on initial treatment with an ACE inhibitor than
a beta-blocker [11]. However, an ACE inhibitor-based regimen may often be associated with the unwanted side-effect cough [13].

It is well known that blood pressure falls during sleep and rises rapidly just before the time of awakening and arising [14, 15]. During these early morning hours, the incidence of coronary artery disease morbidity and mortality is highest [16, 17]. The early morning period is a vulnerable period in terms of therapy since it corresponds to the trough of the effect of most antihypertensive agents and at the same time the period of highest risk. Current knowledge of the pathogenesis and pathophysiology of hypertensive cardiovascular disease indicates that it is important to achieve effective 24-h blood pressure control, with smooth antihypertensive efficacy and reduced blood pressure variability, as well as to attenuate the early morning blood pressure surge, preferably with once-daily dosing [18, 19].

The purpose of the present study was to determine the antihypertensive efficacy, effect duration and safety of the angiotensin II type1 (AT1) receptor blocker candesartan cilexetil and the ACE inhibitor enalapril once daily in patients with mild to moderate hypertension.

METHODS

A multicenter, randomised, double-blind parallel group study comparing the effects of candesartan cilexetil and enalapril was performed in 42 centers in Finland, France, The Netherlands, Spain and Sweden from November 1997 to February 1999. Three-hundred-and-ninety-five men and women in the age range 20–80 years with primary hypertension were included. The major inclusion criteria were a mean sitting diastolic blood pressure of 95–114 mmHg and a 24-h ambulatory blood pressure measurement post-dose completed with an awake mean diastolic ambulatory blood pressure of more than 85 mmHg after 4 weeks of placebo run-in. Recognized contraindications for the drugs were observed.

Following the 4-week single-blind placebo run-in period, patients were randomised to an 8-week double-blind treatment period with either candesartan cilexetil or enalapril. The initial dose was candesartan cilexetil 8 mg once daily or enalapril 10 mg once daily. After 4 weeks, all doses were doubled in a forced dose titration manner. The study design is illustrated in Fig. 1.

Blood pressure and heart rate were measured at trough in the morning, immediately before drug administration. All clinic blood pressure and heart rate measurements were made using a fully automated device (Omron HEM-705-CP). The blood pressure readings were made on the arm with the highest mean sitting diastolic blood pressure, chosen at the first visit. At each visit three consecutive sitting measurements with at least 1-min intervals were made after the patient had rested in a quiet room for a minimum of 5 min. If any of the three measurements of diastolic blood pressure differed by more than 10 mmHg, two extra measurements were taken. The two extreme values were discarded. The mean of three sitting measurements of blood pressure and heart rate were used for analyses.

Non-invasive ambulatory blood pressure was measured with the Spacelab 90207 blood pressure monitor. Ambulatory blood pressure measurements were commenced between 08.00 h and 10.30 h and continued for 36 h. The cuff was placed on the non-dominant arm and blood pressure was registered automatically every 20 min from 06.00 h to 22.00 h, and every 30 min from 22.00 h to 06.00 h. The study drug was taken as soon as the device was confirmed to work properly. The minimum accepted duration of ambulatory blood pressure recording was 24 h after drug intake, otherwise the ambulatory blood
pressure monitoring had to be repeated. Ambulatory blood pressure monitoring was also to be repeated if the quality of the recording was not sufficient. Out-of-range values were removed if the pulse pressure was less than 12 mmHg, systolic blood pressure more than 250 mmHg or less than 60 mmHg, diastolic blood pressure more than 150 mmHg or less than 40 mmHg, pulse more than 200 beats/min or less than 40 beats/min.

The primary efficacy variable was the change in mean diastolic and systolic ambulatory blood pressure 22–24 h post-dose from baseline to after 8 weeks of treatment. Moreover, the changes from baseline to after 8 weeks of treatment in mean daytime ambulatory blood pressure on the day after the last dose was given (06.00 h to 18.00 h, i.e. approximately 24–36 h after dose), mean ambulatory blood pressure 0 to 24 h post-dose and the proportions of responders and controlled patients after 8 weeks were calculated. A patient was considered as a responder if the clinic diastolic blood pressure was $\leq 90$ mmHg and/or a reduction in diastolic blood pressure from baseline of at least 10 mmHg had occurred. Patients were considered to be controlled if the diastolic blood pressure at trough was $\leq 90$ mmHg after 8 weeks of treatment.

The population trough-to-peak ratio, calculated as the ratio of the mean change in ambulatory blood pressure from baseline to week 8 corresponding to peak and trough values is presented descriptively. Peak was defined as the minimum of the mean reductions of hour 5–9 post-dose. The mean trough value was defined as the mean of the 24th hour post-dose.

Adverse events were recorded from spontaneous reports or based on the patient’s response to an open question. As adverse events, any unintended, unfavorable clinical sign or symptom, new illness or disease or deterioration of existing condition, clinical irrelevant deterioration in a laboratory variable or other clinical test whether or not considered treatment related were considered.

Statistical analysis
The primary efficacy variable, the change in mean diastolic and systolic ambulatory blood pressure 22–24 h post-dose from baseline to 8 weeks of treatment, was analysed by multivariate analysis of covariance (MANCOVA), with fixed factors for center and treatment, using baseline values as a covariate in the linear model [20]. Inference on mean treatment effects was based on the multivariate test statistic calculated as a linear hypothesis test from the fitted model. The univariate confidence intervals and $p$-values presented were calculated by using the difference between the least-squares estimates of mean treatment. This estimate and its standard error and the upper 2.5% quintile of Student’s $t$-distribution corresponding to test of contrasts were used to calculate the 95% confidence interval (CI) for the true mean treatment difference. All tests were two-sided.

Univariate analysis of covariates was used for all other ambulatory blood pressure variables with the same factors and covariates as for the primary variable. The proportion of responders and the difference in proportion of controlled patients after 8 weeks were analysed by estimating the odds ratio. The $p$-value was provided from Mantel–Haenszel statistic. A $p$-value < 0.05 was considered significant.

Ethical considerations
The final study protocol was approved by the local ethics committee of all participating centers. Verbal and written informed consent was obtained from all patients. The study was performed in accordance with the Declaration of Helsinki and Principle of Good Clinical Practice.

RESULTS
Three-hundred-and-ninety-five patients were randomised. The intention-to-treat population included 390 patients, since there were no follow-up efficacy data available for five patients. The baseline characteristics of the patients are given in Table I. The two treatment groups were similar with regards to age, race, weight, height, body mass index, medical history, duration of hypertension as well as blood pressure and heart rate.

The mean diastolic and systolic ambulatory blood pressure 22–24 h post-dose decreased over the treatment period in both active treatment groups (Fig. 2). In the candesartan cilexetil group, the adjusted mean change in diastolic ambulatory blood pressure was $-8.7$ mmHg (95% CI: $-10.5$ to $-7.0$ mmHg) and in the enalapril group the adjusted mean change was $-5.8$ mmHg (95% CI: $-7.5$ to $-4.1$ mmHg).

Table I. Baseline characteristics, mean ± standard deviation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Candesartan cilexetil</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>196</td>
<td>194</td>
</tr>
<tr>
<td>Male/Female</td>
<td>123/73</td>
<td>109/85</td>
</tr>
<tr>
<td>Caucasian/Black/Oriental</td>
<td>192/2/2</td>
<td>192/1/1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.5 ± 10.1</td>
<td>55.7 ± 10.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.4 ± 14.4</td>
<td>81.6 ± 15.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.7 ± 10.1</td>
<td>168.7 ± 9.9</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>28.2 ± 4.0</td>
<td>28.6 ± 4.8</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>164.6 ± 16.0</td>
<td>164.3 ± 15.8</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>102.2 ± 6.2</td>
<td>102.1 ± 6.1</td>
</tr>
<tr>
<td>Heart rate</td>
<td>75.0 ± 11.0</td>
<td>77.9 ± 12.4</td>
</tr>
</tbody>
</table>

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
The adjusted mean difference for the change from baseline to week 8 between candesartan cilexetil and enalapril was -3.0 mmHg (95% CI: -5.1 to -0.8 mmHg; \(p < 0.008\)). The corresponding adjusted mean change in systolic ambulatory blood pressure 22–24 h post-dose was -13.5 mmHg (95% CI: -16.1 to -10.9 mmHg) with candesartan cilexetil as compared to -9.9 mmHg (95% CI: -12.6 to -7.3 mmHg) with enalapril. The adjusted mean difference in change between the treatment groups was -3.5 mmHg (95% CI: -6.8 to -0.3 mmHg; \(p < 0.032\)).

On the day after the last given dose (approximately 24–36 h post-dose) patients treated with candesartan cilexetil had an adjusted mean reduction in diastolic ambulatory blood pressure of 8.0 mmHg (95% CI: -9.3 to -6.7 mmHg) measured as compared to an adjusted mean diastolic ambulatory blood pressure reduction of 4.5 mmHg (95% CI: -5.9 to -3.2 mmHg) in the enalapril group (Fig. 3). The adjusted mean difference in change between the groups was -3.5 mmHg (95% CI: -5.1 to -1.8 mmHg; \(p < 0.001\)). The corresponding change in systolic ambulatory blood pressure was -11.4 mmHg (95% CI: -13.5 to -9.3 mmHg) with candesartan cilexetil as compared to -7.2 mmHg (95% CI: -9.4 to -5.1 mmHg) with enalapril (Fig. 3). The difference between the two treatments was -4.2 mmHg (95% CI: -6.8 to -1.6 mmHg; \(p < 0.002\)).

In Table II the adjusted mean change from baseline in clinic blood pressure and heart rate 24 h post-dose following 4 weeks and 8 weeks treatment are given. Figure 4 illustrates the time profiles for mean changes from baseline to 8 weeks in diastolic ambulatory blood pressure over 36 h post-dose, while the corresponding time profiles for mean changes in systolic ambulatory blood pressure are given in Fig. 5. The mean ambulatory blood pressure in the first 24 h following the dose did not differ significantly between the two treatment groups. In the candesartan cilexetil group, adjusted mean diastolic blood pressure fell by -8.4 mmHg (95% CI: -9.6 to -7.2 mmHg) as compared to -7.9 mmHg (95% CI: -9.2 to -6.7 mmHg) in the enalapril group. The corresponding changes in mean systolic ambulatory blood pressure was -13.1 mmHg (95% CI: -14.9 to -11.2 mmHg) with candesartan cilexetil as compared to -12.7 mmHg (95% CI: -14.6 to -10.9 mmHg) with enalapril. There were no significant differences in awake ambulatory blood pressure (\(p > 0.2\)). Calculated trough-to-peak ratio was 0.76 for candesartan cilexetil and 0.38 for enalapril.

There were no statistically significant differences in the proportion of responders’ or patients’ blood pressure control following 8 weeks of active treatment. In the candesartan cilexetil group 57.8% (95% CI: 50.7–64.8%) were responders as compared to 50.0% (95% CI: 42.6–57.4%) in the enalapril group (\(p = 0.139\)). The proportion of controlled patients’ control was 44.4% (95% CI: 37.3–
51.5%) in the candesartan cilexetil group and 39.2% (95% CI: 32.0–46.4%) in the enalapril group ($p > 0.2$).

During the 4 weeks single-blind placebo run-in period, approximately one-third of the patients reported at least one adverse event, with very similar pattern among patients later randomised to candesartan cilexetil and enalapril, 36.5% and 35.5%, respectively. During the 8-week double-blind treatment period the proportion of patient reporting at least one adverse event was 47.2% in the candesartan cilexetil group and 56.3% in the enalapril group. The most common adverse events are summarized in Table III. The proportion of patients who stopped the drug due to an adverse event was 2.0% with candesartan cilexetil and 3.6% with enalapril. For 11 patients the treatment with randomised investigational drug was stopped due to adverse events. Of these patients, four were treated with candesartan cilexetil while seven patients were treated with enalapril. In the candesartan cilexetil group, one patient experienced angioedema. No major change was seen for any laboratory variable in any of the treatment groups during the double-blind treatment period.

**DISCUSSION**

The present 8-week multicenter, randomised, double-

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**Table II. Clinic blood pressure and heart rate; adjusted mean and 95% confidence interval for each treatment for the change ($\Delta$) from baseline to week 4 and week 8, respectively**

<table>
<thead>
<tr>
<th></th>
<th>Candesartan cilexetil</th>
<th>Enalapril</th>
<th>Difference</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$SBP, week 4 (mmHg)</td>
<td>$-13.8 (-16.1 to -11.4)$</td>
<td>$-9.6 (-12.0 to -7.1)$</td>
<td>$-4.2 (-7.1 to -1.3)$</td>
<td>0.004</td>
</tr>
<tr>
<td>$\Delta$DBP, week 4 (mmHg)</td>
<td>$-8.8 (-10.2 to -7.4)$</td>
<td>$-6.6 (-8.0 to -5.2)$</td>
<td>$-2.2 (-3.9 to -0.5)$</td>
<td>0.01</td>
</tr>
<tr>
<td>$\Delta$HR, week 4 (bpm)</td>
<td>0.4 (-1.0 to 1.7)</td>
<td>-0.5 (-1.8 to 0.9)</td>
<td>0.8 (-0.8 to 2.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>$\Delta$SBP, week 8 (mmHg)</td>
<td>$-15.7 (-18.4 to -13.1)$</td>
<td>$-11.6 (-14.3 to -8.8)$</td>
<td>$-4.2 (-7.4 to -0.9)$</td>
<td>0.013</td>
</tr>
<tr>
<td>$\Delta$DBP, week 8 (mmHg)</td>
<td>$-9.8 (-11.3 to 8.2)$</td>
<td>$-7.2 (-8.8 to -5.6)$</td>
<td>$-2.5 (-4.5 to -0.6)$</td>
<td>0.009</td>
</tr>
<tr>
<td>$\Delta$HR, week 8 (beats/min)</td>
<td>0.0 (-1.5 to 1.4)</td>
<td>-1.5 (-3.0 to 0.0)</td>
<td>1.5 (-0.3 to 3.2)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; n.s., not significant.

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**Fig. 4.** Time profiles for mean changes from baseline to eight weeks in diastolic ambulatory blood pressure over 36 h post-dose.
blind parallel group study comparing the effects of candesartan cilexetil and enalapril using a forced dose titration design demonstrates that candesartan cilexetil 16 mg once daily was significantly more effective in reducing blood pressure at trough than enalapril 20 mg once daily. The differences between treatments were seen at clinic visits already after an initial 4-week treatment period with candesartan cilexetil 8 mg or enalapril 10 mg. On the day after the last dose, candesartan cilexetil was also more effective in controlling blood pressure than enalapril. However, the proportion of responders or controlled patients by given treatment did not differ between the groups. Both drugs were generally well tolerated, although there were twice as many patients who experienced cough in the enalapril group and one patient in the candesartan cilexetil group who developed angioedema.

The AT1-receptor antagonists are the latest major group of antihypertensive drugs to become generally available [2]. In contrast to the ACE inhibitors [11–13], the effects of AT1-receptor antagonists on cardiovascular risk in patients with hypertension has not been assessed. However, the AT1-receptor antagonists have generally few side-effects and it has been suggested that this may encourage adherence to therapy [2]. The primary efficacy variable in the present study was the change in mean diastolic and systolic ambulatory blood pressure at trough, i.e. 22–24 h post-dose from baseline to after 8 weeks of treatment. The results demonstrate that candesartan cilexetil 16 mg once daily was significantly more effective in reducing blood pressure at trough than enalapril 20 mg once daily. During daytime, i.e. from dose intake until 22.00 h, there was no difference in blood pressure response to the drugs. However, at trough, candesartan cilexetil was superior to enalapril, also illustrated by the trough-to-peak ratios of 0.76 for candesartan cilexetil and 0.38 for enalapril. Obviously, there is a difference in the effect duration of the drugs, despite the fact that their elimination half-lives are of the same magnitude [21, 22]. It has been suggested that the long duration of the antihypertensive effect may be

**Table III. Number (%) of patients by the most common adverse events (≥2% in any treatment group)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Candesartan cilexetil</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>30 (15.2)</td>
<td>32 (16.2)</td>
</tr>
<tr>
<td>Infection viral</td>
<td>9 (4.6)</td>
<td>18 (9.1)</td>
</tr>
<tr>
<td>Coughing</td>
<td>7 (3.6)</td>
<td>15 (7.6)</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>7 (3.6)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Bronchitis/bronchitis aggr.</td>
<td>4 (2.0)</td>
<td>5 (2.5)</td>
</tr>
</tbody>
</table>
related to the long-lasting and insurmountable binding of candesartan cilexetil to the AT1-receptor [23, 24].

Lower doses of candesartan cilexetil have been compared to enalapril in previous studies [25–27]. Zanchetti and co-workers found candesartan cilexetil and enalapril to be of equivalent efficacy in patients with mild to moderate hypertension [25]. The starting dose for candesartan cilexetil was 4 mg compared to 10 mg enalapril or placebo. In contrast to the present study, the dosage was doubled after 4 weeks of treatment only in non-responders. After 4 weeks, dose doubling was necessary in 43.2% of patients in the placebo group, 36.7% in the candesartan cilexetil group and 28.2% in the enalapril group. In another double-blind, randomised, multicenter placebo-controlled study, the effects of candesartan cilexetil 4 mg, 8 mg or 12 mg were compared to enalapril 10 mg [26]. After 12 weeks treatment, significant reductions in mean sitting diastolic blood pressure was seen for patients who received candesartan cilexetil 8 mg, 12 mg or enalapril 10 mg. The blood pressure-reducing effect of candesartan cilexetil 8 mg was similar to that achieved with enalapril 10 mg, which provides a rationale for the initial dose chosen in the present study.

Previous studies have demonstrated a dose-dependent antihypertensive effect of candesartan cilexetil [28]. In agreement with the results of the present study, one previous 12 week comparative trial reported that candesartan cilexetil lowers blood pressure more effectively than enalapril [27]. In that study the initial dose of candesartan cilexetil was 8 mg and the initial dose of enalapril was 10 mg. In contrast to the present study, however, the dose was doubled only in patients with a diastolic blood pressure of more than 90 mmHg after 6 weeks treatment. Both the present and the previous study demonstrated that candesartan cilexetil 8 mg was more effective than enalapril 10 mg. Dose increments resulted in further blood pressure reduction with both treatments while the difference between treatments remained of the same magnitude.

The superior efficacy of candesartan cilexetil at trough demonstrated in the present study is of particular interest in relation to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [1]. According to their recommendation, an optimal formulation should provide 24-h efficacy with a once-daily dose, with at least 50% of the peak effect remaining at the end of the 24 h. Moreover, it is stated that agents with a duration of action beyond 24 h are attractive because many patients inadvertently miss at least one dose of medication each week [1]. In the present study, when ambulatory blood pressure was monitored for 36 h, a statistically significant difference in blood pressure reduction was observed from 0.24 to 36 h, corresponding to the clinically relevant situation of a missed dose. On the day of the missed dose, candesartan cilexetil reduced blood pressure by 11.4/8.0 mmHg as compared to 7.2/4.5 mmHg for enalapril. The difference between the two drugs seems to increase during the day of the missed dose as illustrated in Figs 4 and 5.

Lacourcière and co-workers compared the antihypertensive effect duration of the two AT1-receptor blocker losartan and candesartan cilexetil [29]. The study design was similar to that in the present study, with an 8-week treatment period and forced doubling of doses after 4 weeks. Candesartan cilexetil 16 mg reduced ambulatory blood pressure significantly more than losartan 100 mg when measured during the entire 36-h observation period.

It may be argued that there may be some limitations in relation to the method used to evaluate tolerance of the drugs in the present study, e.g. no precise written questions were used and the total number of side-effects were few. However, both drugs were well tolerated and adverse events leading to discontinuation were few. Of note is that cough occurred in twice as many patients on enalapril as compared to candesartan cilexetil. Cough is a well-known side-effect of ACE inhibitor treatment [30, 31]. In the recently published Swedish Trial on Old Patients with Hypertension-2, cough was reported in 30% of ACE inhibitor-treated patients [13]. Several studies have shown that cough is less likely to occur with an angiotensin II receptor blocker when patients with previous ACE inhibitor induced cough are treated either with an AT1-receptor blocker or an ACE inhibitor [32–35]. Angioedema has been reported as an uncommon but serious side-effect of ACE inhibitors [36, 37]. It has been estimated to occur in one case per 6300 patient-years, and usually appears within the first 3 weeks after starting treatment with an ACE inhibitor [37]. In the present study, a 42-year-old man experienced a clinically diagnosed angioneurotic edema after 26 days treatment with candesartan cilexetil. Angioedema has previously been reported in the association with the use of other AT1-receptor blockers [38, 39]. Among 98 spontaneously reported cases of angioedema, 94 cases were in relation to ACE inhibitors and four cases in relation to AT1-receptor blockers in a recent report from the Swiss Drug Monitoring Centre [40]. The rare cases of angioedema induced by AT1-receptor antagonists were usually milder and in two of the four reported cases angioedema recurred after switching from an ACE inhibitor to an AT1-receptor blocker. A possible explanation for the association between angioedema and AT1-receptor antagonists may be the observation that the stimulation of the AT-2 receptor mediates vasodilation by an autocrine cascade including bradykinin [41].

A limitation of the present study relates to the doses
used. Thus, the conclusions drawn from the present comparison are relevant only to the doses chosen. Although the doses used in the present study appear just to compare, it cannot be excluded that other doses of the agents may have given a different result, at least with regard to the observation in mean diastolic and systolic ambulatory blood pressure 22–24 h post-dose. Previous studies with ACE inhibitor have indicated that an increased dose are not only accompanied by an increased effect at peak, but also an increased duration of blood pressure reduction [42].

In conclusion, the present study suggests that several advantages may be attributed to use of candesartan cilexetil, as compared enalapril in treatment of patients with essential hypertension. In comparison with enalapril 20 mg, candesartan cilexetil 16 mg more effectively lowered blood pressure at trough and in particular on the day of a missed dose. The value of ACE inhibitors in relation to a reduced cardiovascular risk in patients with hypertension has recently been demonstrated [11–13]. This important aspect is currently investigated for candesartan cilexetil in the SCOPE trial [43].

ACKNOWLEDGEMENTS

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