Efficacy of Candesartan Cilexetil Alone or in Combination With Amlodipine and Hydrochlorothiazide in Moderate-to-Severe Hypertension

Graham A. MacGregor, J. Reuven Viskoper, Tarek F.T. Antonios, Feng J. He, on behalf of the UK and Israel Candesartan Investigators

Abstract—This multicenter study evaluated the efficacy of candesartan cilexetil, an angiotensin II type 1 receptor antagonist, used alone or in combination with amlodipine or in combination with amlodipine and hydrochlorothiazide in the treatment of patients with moderate-to-severe essential hypertension. After a 2-week, single-blind, placebo run-in period, patients entered a 12-week, open-label, dose-titration period. The candesartan cilexetil dose was increased from 8 to 16 mg once daily; amlodipine (5 mg once daily), hydrochlorothiazide (25 mg once daily), and additional medication were also added sequentially if necessary. Patients then entered a final 4-week, parallel-group, double-blind, randomized, placebo-controlled withdrawal period of candesartan alone. A total of 216 patients were recruited. After a 2-week run-in period on placebo tablets, mean sitting blood pressure (BP) was 175/108 mm Hg. At the end of the 12-week dose-titration/maintenance period, mean sitting BP fell to 141/88 mm Hg. In 67 patients who were randomized to placebo and had their candesartan withdrawn, there was a highly significant increase in mean systolic/diastolic BP (13/6 mm Hg) compared with those patients who continued with candesartan (ANCOVA, $P<0.0001$). In conclusion, candesartan cilexetil is an effective BP-lowering drug when used alone or in combination with amlodipine or amlodipine plus hydrochlorothiazide in the treatment of moderate-to-severe essential hypertension. The drug was well tolerated throughout the investigation period. (Hypertension. 2000;36:454-460.)

Key Words: candesartan cilexetil ■ amlodipine ■ hydrochlorothiazide ■ hypertension, essential ■ angiotensin II receptors antagonists

The treatment of severe hypertension is often difficult, and multiple antihypertensive agents are often required.1,2 Studies suggest that antihypertensive monotherapy generally controls blood pressure (BP) in only 50% to 60% of patients.3 Angiotensin II type 1 receptor antagonists are a relatively new class of antihypertensive agents. In patients with mild-to-moderate hypertension, angiotensin II antagonists have been shown to lower BP as effectively as angiotensin-converting enzyme inhibitors.4 However, their role and efficacy in more severe hypertension has not been properly assessed. Although several studies have shown promising results with angiotensin II antagonists in this setting,5,6 these were not placebo-controlled studies; therefore, it is impossible to be certain that the fall in BP that occurs is related to the activity of the drug itself and not related to other drugs that were subsequently added.

Candesartan is a selective long-acting angiotensin II type 1 receptor antagonists. The drug is administered orally as candesartan cilexetil, an ester prodrug that is rapidly and completely converted to the active moiety during gastrointestinal absorption.7 Double-blind placebo-controlled studies have shown candesartan cilexetil to be efficacious and well tolerated in patients with mild-to-moderate essential hypertension.8,9 The drug has shown additive antihypertensive effects when combined with the thiazide diuretic, hydrochlorothiazide.10

The present multiphase study investigated the efficacy of candesartan in patients with moderate-to-severe essential hypertension who either had not received previous treatment or had previous treatment that was not controlling their blood pressure. Candesartan was initially used alone; then, if necessary, amlodipine was added, followed by the addition of a diuretic. When BP was controlled, the contribution of candesartan to BP control was assessed by double-blind withdrawal of candesartan.

Methods

Male and female patients with well-documented moderate-to-severe essential hypertension (sitting diastolic BP [DBP] $>100$ mm Hg) who were either untreated or unsatisfactorily treated were included in the present study. Females of child-bearing potential and patients...
with malignant hypertension, secondary hypertension, significant cardiac, hepatic, renal, or cerebrovascular disease, insulin-dependent diabetes mellitus, or other serious illness were excluded from the study. The protocol was approved by the local medical ethics committees at each center. Informed written consent was obtained from each patient.

**Study Design**

The present trial was a prospective multicenter study conducted in 14 centers in the United Kingdom and 4 centers in Israel. The study consisted of 3 periods (Figure 1). First, eligible patients entered a single-blind placebo run-in period of up to 2 weeks. Patients meeting the definition of moderate-to-severe hypertension during and at the end of this period entered an open-label, response-dependent, dose-titration period of up to 12 weeks. If the DBP reached $\geq 110$ mm Hg at any time during the run-in period, the investigator could begin the dose-titration period, providing that the patient had received at least 3 days of placebo treatment. It was mandatory to begin active treatment if the DBP exceeded $115$ mm Hg. The candesartan dose was titrated according to individual responses. There were 5 titration steps at 2-week intervals (Figure 1), with the aim being to control sitting DBP to $95$ mm Hg. All patients initially received candesartan (8 mg once daily). This was increased to $16$ mg once daily if BP control was not achieved. If necessary, amlopidine (5 mg once daily) was then added, followed by hydrochlorothiazide ($25$ mg once daily). If the DBP was $\geq 110$ mm Hg at any time during the titration period, patients proceeded to the next titration step (provided that they received at least 3 days of treatment at a specified dosing regimen). Once the DBP was controlled (ie, $<95$ mm Hg), patients remained on the same maintenance dose for the remainder of the dose-titration period. Patients whose DBP could not be controlled by dose titration to $<95$ mm Hg or whose DBP subsequently became unstable ($\geq 100$ mm Hg) during maintenance treatment were, at the investigator’s discretion, either withdrawn from the study or given additional antihypertensive medication. In the latter circumstance, all other study procedures were uninterrupted, and candesartan cilexetil was administered continuously. These patients were termed the special (or S) group, and their results are presented separately.

Patients who completed the dose-titration period and whose DBP was controlled to $<95$ mm Hg and had not exceeded $99$ mm Hg during the maintenance treatment period entered a 4-week, randomized, double-blind withdrawal period. S group patients entered the withdrawal period if their DBP was $\leq 99$ mm Hg at the end of maintenance period. Patients were randomized, with the use of a computer-generated code, to receive either their maintenance candesartan dose or a matching placebo. Concomitant amlopidine and hydrochlorothiazide were continued unchanged. Compliance with study medication was checked by counting returned tablets.

**BP Measurements**

Patients were assessed at 2 weekly clinic visits throughout the study. BP measurements were performed after patients had at least 10 minutes of rest and immediately before administration of the study medication; the validated semiautomatic oscillometric device OM-RON HEM705CP (Hutchings Health Care Ltd) was used for the measurements. All measurements for an individual were taken irrespective of their causal relation to the study drug.

**Laboratory Tests**

Blood and urine samples were obtained at selected times throughout the study. Variables measured were serum electrolytes, urea, creatinine, uric acid, glucose, total cholesterol, triglycerides, and full blood count. Plasma renin activity (PRA) and aldosterone were measured by radioimmunoassay. All adverse experiences that were reported by patients or observed by the investigator were recorded by patients or observers. These were termed the special (or S) group.

**Statistical Analysis**

Data from the dose-titration period were analyzed on an intent-to-treat basis. Data from the withdrawal period were analyzed on an intent-to-treat basis and a per protocol basis (which included completion of this period by the patients with no major protocol violations). Data from S group were presented separately. All results are given as mean±SEM.

The overall response rate at the end of dose-titration period was calculated as the proportion of patients with DBP$<95$ mm Hg. DBP and systolic BP (SBP) changes from baseline were also presented. Both of these analyses were stratified according to the treatment taken at the end of this period. During the double-blind withdrawal period, continuous data were analyzed by 2-tailed unpaired or paired
A total of 216 patients entered the run-in period. Thirty-one patients were withdrawn at the end of this period because of adverse events (n = 5), death (n = 5), and other reasons (n = 3). The remaining 159 patients (of whom 28 were S group patients) were randomized to continue treatment with candesartan cilexetil (n = 77) or to receive placebo (n = 82). Five patients subsequently withdrew during this period: 3 from the candesartan cilexetil group (all because of adverse events) and 2 from the placebo group (because of lack of efficacy or other reasons). Thus, 154 patients (74 candesartan cilexetil, 80 placebo) completed the study. Table 1 shows baseline characteristics of all study patients. The demographic characteristics of the patients remained similar at each stage of the study and did not differ importantly between the randomized withdrawal treatment groups. The 185 patients (130 males, 55 females) who began the dose-titration period had a mean age of 54.7 years. The mean duration of hypertension was 9.7 years.

### Analysis of Efficacy

#### Dose-Titrination Period

At the end of the dose-titration period, 31 patients (19.1% of the 162 patients completing this period) were treated with candesartan cilexetil (8 mg); 25 (15.4%), with candesartan (16 mg); 47 (29.0%), with candesartan cilexetil (16 mg) plus amlodipine (5 mg); and 29 (17.9%), with candesartan cilexetil (16 mg) plus amlodipine (5 mg) and hydrochlorothiazide (25 mg). The remaining 30 (18.5%) were given additional therapy and were classified as S group patients.

The overall mean sitting DBP was reduced in this open part of the study by 19.8 mm Hg, from 107.8 ± 0.4 mm Hg at baseline to 88.0 ± 0.6 mm Hg at the end of the dose-titration period (Figure 2). Overall mean sitting SBP was reduced by 32.9 mm Hg, from 174.4 ± 1.3 mm Hg at baseline to 141.5 ± 1.2 mm Hg. A comparable pattern was observed across the subgroups. For both DBP and SBP, changes in sitting measurements showed a pattern similar to that of the sitting measurements, with slightly higher absolute values.

#### Withdrawal Period

With the exclusion of the S group, 131 patients were randomized to either continue candesartan cilexetil treatment (n = 64) or receive placebo (n = 67). At the end of double-blind withdrawal period, the mean sitting DBP increased significantly (by 7.1 ± 1.0 mm Hg, P < 0.0001) in the placebo group (Table 2, Figure 2). In contrast, there was no significant change in the candesartan cilexetil group (+0.6 ± 1.0 mm Hg, P = 0.2735). ANCOVA showed the difference between the treatment groups to be statistically significant (P < 0.0001).

### Results

A total of 216 patients entered the run-in period. Thirty-one patients were withdrawn at the end of this period because their DBP was <100 mm Hg. Therefore, 185 patients entered the dose-titration period, and 162 completed it. Twenty-six patients were withdrawn during or at the end of this period because of adverse events (n = 5), death (n = 1), and other reasons (n = 3) or because they were lost to follow-up (n = 3). The remaining 159 patients (of whom 28 were S group patients) were randomized to continue treatment with candesartan cilexetil (n = 77) or to receive placebo (n = 82). Five patients subsequently withdrew during this period: 3 from the candesartan cilexetil group (all because of adverse events) and 2 from the placebo group (because of lack of efficacy or other reasons). Thus, 154 patients (74 candesartan cilexetil, 80 placebo) completed the study. Table 1 shows baseline characteristics of all study patients. The demographic characteristics of the patients remained similar at each stage of the study and did not differ importantly between the randomized withdrawal treatment groups. The 185 patients (130 males, 55 females) who began the dose-titration period had a mean age of 54.7 years. The mean duration of hypertension was 9.7 years.

### Table 1. Baseline Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Population</th>
<th>Withdrawal Period Completers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enrolled (N=216)</td>
<td>Start of Dose Titration (N=185)</td>
</tr>
<tr>
<td>Age, y</td>
<td>54.6±0.7</td>
<td>54.7±0.7</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>151 (70)</td>
<td>130 (70)</td>
</tr>
<tr>
<td>Women</td>
<td>65 (30)</td>
<td>55 (30)</td>
</tr>
<tr>
<td>Ethnic group, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>197 (91)</td>
<td>170 (92)</td>
</tr>
<tr>
<td>Black</td>
<td>14 (6)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.8±1.0</td>
<td>82.2±1.1</td>
</tr>
<tr>
<td>BMI, % (kg/m²)</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Sitting BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>171.9±1.2</td>
<td>174.4±1.3</td>
</tr>
<tr>
<td>DBP</td>
<td>106.8±0.3</td>
<td>107.8±0.4</td>
</tr>
</tbody>
</table>

Values are mean ± SE or number (percentage) of patients. BMI indicates body mass index.
Patients in whom placebo was substituted for candesartan cilexetil monotherapy (8 mg or 16 mg) showed a mean increase of 9.5±1.8 mm Hg in DBP, whereas those who continued active monotherapy showed an increase of only 1.3±1.6 mm Hg. Mean changes in sitting SBP showed a pattern comparable to the mean changes in DBP. There was a mean increase of 12.5±2.8 mm Hg in SBP in the placebo group (least squares method, \(P<0.0001\)) and a decrease of 1.1±2.2 mm Hg in the candesartan cilexetil group (\(P=0.7104\)); the difference between the groups was statistically significant (ANCOVA, \(P<0.0001\)). Analysis of the per protocol population, or inclusion of the S group patients, showed no important differences to the intention-to-treat analysis with regard to the changes in DBP and SBP.

### Ambulatory Blood Pressure Monitoring

ABPM was performed at the beginning and end of the withdrawal period for 106 patients, of whom 86 had responded to dose titration and 20 belonged to the S group. Excluding the S group, mean baseline 24-hour DBP was 78.8±1.1 mm Hg in the placebo group (n=48) and 81.7±1.2 mm Hg in the candesartan cilexetil group (n=38). Four weeks later, there was no change in mean DBP in the candesartan cilexetil group compared with an increase of 6.4±0.92 mm Hg in the placebo group (Figure 3). The difference between the groups was statistically significant (\(P=0.0001\)) and remained so if the S group was included in the analysis. The difference between candesartan cilexetil and placebo treatment in the withdrawal period was also statistically significant in the groups treated with 8 mg candesartan cilexetil (+10 mm Hg, \(P=0.0065\)), 16 mg candesartan cilexetil (+7.6 mm Hg, \(P=0.0063\)), or triple therapy (+7.2 mm Hg, \(P=0.0205\)) during dose titration. A similar pattern of results was observed in the changes in SBP, with significantly greater increases occurring in placebo recipients than in those continuing treatment with 8 mg candesartan cilexetil or triple therapy (\(P<0.05\)).

### PRA and Aldosterone

After 4 weeks of withdrawal of candesartan cilexetil, there was a decrease of 1.94 ng/mL per hour in mean PRA in placebo recipients compared with no change in patients who continued treatment with candesartan cilexetil (\(P=0.017\) between the groups, Figure 2). Mean plasma aldosterone levels increased in the placebo group (by 68 pmol/L) and in the active treatment group (by 31 pmol/L), but the difference was not statistically significant between groups. In the placebo group, there was a significant correlation between the level of PRA at the end of withdrawal of candesartan cilexetil and the rise in DBP \((r=0.21, P=0.06)\) and SBP \((r=0.29,\)
P, 0.05; Figure 4) that occurred on stopping candesartan. By multivariate analysis, the PRA level at the end of withdrawal was still a significant predictor of the rise in SBP in the placebo group after adjusting for age, gender, race, and body mass index. No similar correlation was found for the change in plasma aldosterone levels.

Tolerability
A total of 87 (47.0%) of 185 patients experienced a total of 219 adverse events during the dose-titration period. The most frequently observed adverse event during this period was headache, followed by upper respiratory tract infection, tiredness, increase in plasma creatinine kinase levels, dizziness, lethargy, and cough. Only 13 adverse events (5.9%) were classified as probably or definitely related to study treatment. During the double-blind withdrawal period, 41 (25.8%) of 159 patients experienced a total of 71 adverse events. There was no statistically significant difference in the proportion of patients who experienced adverse events during treatment with candesartan cilexetil (24 of 77, 31.2%) or placebo (17 of 82, 20.7%; P = 0.1327). Again, headache was the most frequent adverse event. Only 4 (5.6%) of the 71 adverse events were classified as probably or definitely related to study treatment. Adverse events were the primary cause of withdrawal of 10 patients from the study and a secondary cause of the withdrawal of 5 others.

Figure 3. ABPM results before and 4 weeks after withdrawal of candesartan in the group of patients who were randomized to take placebo and have their candesartan treatment withdrawn.

Table 2. Effect of Treatment on SBP and DBP

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Candesartan</th>
<th>Adjusted Difference (Placebo vs Candesartan)</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan 8 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>137±4</td>
<td>155±4</td>
<td>18*</td>
<td>140±5</td>
</tr>
<tr>
<td>DBP</td>
<td>87±2</td>
<td>99±2</td>
<td>12†</td>
<td>86±2</td>
</tr>
<tr>
<td>16 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>138±4</td>
<td>144±5</td>
<td>6‡</td>
<td>145±5</td>
</tr>
<tr>
<td>DBP</td>
<td>86±3</td>
<td>91±4</td>
<td>5‡</td>
<td>90±2</td>
</tr>
<tr>
<td>16 mg + amlodipine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>143±3</td>
<td>154±3</td>
<td>11†</td>
<td>143±2</td>
</tr>
<tr>
<td>DBP</td>
<td>87±1</td>
<td>92±2</td>
<td>5*</td>
<td>90±1</td>
</tr>
<tr>
<td>16 mg + amlodipine + HCTZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>144±3</td>
<td>155±4</td>
<td>11‡</td>
<td>138±4</td>
</tr>
<tr>
<td>DBP</td>
<td>91±2</td>
<td>98±3</td>
<td>7*</td>
<td>85±1</td>
</tr>
<tr>
<td>S group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>139±3</td>
<td>154±3</td>
<td>15‡</td>
<td>143±5</td>
</tr>
<tr>
<td>DBP</td>
<td>88±2</td>
<td>96±3</td>
<td>8*</td>
<td>88±3</td>
</tr>
</tbody>
</table>

Values are mean±SE. HCTZ indicates hydrochlorothiazide. Adjusted differences refer to the differences between the 2 treatment groups in the changes in BP during the double-blind withdrawal period after adjusting for baseline BP. Adjusted P values represent comparisons between the 2 treatment groups after adjusting for the effect of baseline BP.

* P <0.01, †P <0.001, and ‡P <0.05 vs prewithdrawal BPs within each treatment group.
cilexetil monotherapy resulted in a rise in DBP of 9.5 mm Hg compared with a rise of just 1.3 mm Hg in patients who remained on active treatment. However, the substitution of placebo for candesartan cilexetil within the combination regimens resulted in smaller increases. This may be explained by the fact that patients in the combination regimen groups did not respond adequately enough to candesartan monotherapy in the first place.

The ABPM data obtained in the present study support other evidence indicating that candesartan cilexetil has a 24-hour duration of action. The fall in PRA in the group in whom candesartan was withdrawn is the reverse of the rise in PRA seen on starting an angiotensin II type 1 receptor antagonist. This results from the inhibition of the negative feedback of angiotensin II on renin release. The significant relationship between the level of PRA after the withdrawal of candesartan and the BP increase that occurred with stopping candesartan supports the concept that the activity of the renin-angiotensin system is predictive of the antihypertensive response of candesartan.

Indeed the PRA level at the end of withdrawal was still a significant predictor of the rise in systolic BP in the group in whom candesartan was withdrawn after adjusting for age, gender, race, and body mass index. This is the first observation of such a relationship in a relatively large number of hypertensive subjects. The lack of a significant change in plasma aldosterone levels on withdrawal of candesartan concurs with other observations that angiotensin II type 1 receptor antagonists do not appear to affect aldosterone levels. In contrast, angiotensin-converting enzyme inhibitors usually lower aldosterone levels.

In conclusion, candesartan cilexetil is efficacious in the treatment of moderate-to-severe essential hypertension. The drug can be effectively combined with calcium channel blockers and/or diuretics in patients whose hypertension is resistant to monotherapy.

Discussion

The present study demonstrates that candesartan cilexetil is an effective antihypertensive monotherapy in many patients with moderate-to-severe essential hypertension. Moreover, the drug is also effective in combination with either amlopidine and hydrochlorothiazide in patients who do not respond to monotherapy.

The use of a double-blind withdrawal study, once BP has been controlled in these more resistant patients, has been used infrequently in the past but has several advantages in that it allows the efficacy of a single treatment to be assessed by itself and in conjunction with other therapy. Most previous dose-titration studies of other angiotensin II type 1 receptor antagonists in moderate-to-severe hypertension have used an uncontrolled open-label design. Such studies cannot exclude the possibility that reductions in BP could be due to repeated measurements or to other drugs added within combination regimens. In contrast, the present study concluded with a randomized, double-blind, placebo-controlled withdrawal period to allow an unbiased assessment of the effect of candesartan cilexetil in controlling BP. The antihypertensive contribution of candesartan cilexetil is clearly shown by data from the withdrawal period, in which the drug effectively maintained the BP control achieved after dose titration, whereas the placebo did not. Overall, substitution of a placebo for candesartan cilexetil monotherapy or combination therapy resulted in statistically significant increases in mean DBP and SBP after 4 weeks, whereas no significant changes occurred in patients who continued candesartan cilexetil treatment. Substitution of placebo for candesartan cilexetil monotherapy resulted in a rise in DBP of 9.5 mm Hg compared with a rise of just 1.3 mm Hg in patients who remained on active treatment. However, the substitution of placebo for candesartan cilexetil within the combination regimens resulted in smaller increases. This may be explained by the fact that patients in the combination regimen groups did not respond adequately enough to candesartan monotherapy in the first place.

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Appendix

In addition to the authors, the UK and Israel Candesartan Investigator Group includes the following individuals and institutions. From Israel: Prof Shmuel Oren, University of Tel-Aviv, Institute of Preventive Cardiology; Prof Joseph B. Rosenfeld and Dr G Bott-Kanner, University of Tel-Aviv, Institute of Clinical Epidemiology; and Prof Reuven Zimlichman and Dr Bernard I. Chazan, Edith Wolfson Medical Center, Department of Medicine. From the United Kingdom: Dr Henry L. Elliott, University of Glasgow, Department of Medicine and Therapeutics; Prof Peter C. Rubin, University of Nottingham, Therapeutics Department; Dr Peter R. Jackson and Dr Erica J. Wallis, Royal Hallamshire Hospital, Clinical Pharmacology and Therapeutics; Prof Peter S. Sever, Imperial College of Medicine, St. Mary’s Hospital; Prof Peter C. Rubin, University of Nottingham, Therapeutics Department; Prof Peter R. Jackson and Dr Erica J. Wallis, Royal Hallamshire Hospital, Clinical Pharmacology and Therapeutics; Prof Peter S. Sever, Imperial College of Medicine, St. Mary’s Hospital; Prof David J. Webb, University of Edinburgh, Department of Medical Sciences; Dr John Webster, University of Aberdeen, Department of Medicine and Therapeutics; and Prof Robert Wilkinson, Freeman Hospital, Department of Pharmacology.
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