A large-scale, 8-week, open-label, clinical experience trial evaluated the efficacy of the angiotensin II receptor (AT₁ subtype) blocker candesartan cilexetil (16 to 32 mg once daily) either alone or as add-on therapy in 6465 hypertensive patients. The study population was 52% female and 16% African American with a mean age of 58 years. It included 5446 patients who had essential hypertension (HBP) and 1014 patients who had isolated systolic hypertension (ISH). These patients had either untreated or uncontrolled hypertension (systolic blood pressure [SBP] 140 to 179 mm Hg or diastolic blood pressure [DBP] 90 to 109 mm Hg inclusive at baseline) despite a variety of antihypertensive medications including diuretics, calcium antagonists, angiotensin converting enzyme (ACE) inhibitors, and α- or β-blockers, either singly or in combination. The mean baseline blood pressure for the HBP group was 156/97 mm Hg. Candesartan cilexetil as monotherapy (in 51% of HBP patients) reduced mean SBP/DBP by 18.7/13.1 mm Hg. As add-on therapy (in 49% of HBP patients) to various background therapies, candesartan cilexetil consistently reduced mean SBP/DBP further, irrespective of the background therapy: diuretics (17.8/11.3 mm Hg), calcium antagonists (16.6/11.2 mm Hg), β-blockers (16.5/10.4 mm Hg), ACE inhibitors (15.3/10.0 mm Hg), and α-blockers (16.4/10.4 mm Hg). The mean baseline blood pressure for the ISH group was 158/81 mm Hg. Candesartan cilexetil, as monotherapy (in 34% of ISH patients), reduced SBP/DBP by 17.0/4.4 mm Hg. As add-on therapy (in 66% of ISH patients) to various background therapies, candesartan cilexetil consistently reduced mean SBP/DBP further, irrespective of the background therapy: diuretics (17.4/5.1 mm Hg), calcium antagonists (15.6/3.6 mm Hg), β-blockers (14.0/4.8 mm Hg), ACE inhibitors (13.4/4.3 mm Hg), and α-blockers (11.6/4.5 mm Hg). The further blood pressure lowering effects of candesartan cilexetil as add-on therapy were seen regardless of age, sex, and race. Overall, 6.8% of the 6465 patients withdrew because of adverse events, most commonly headache (6.3%) and dizziness (5.0%). Orthostatic hypotension was infrequent; 0.2% with candesartan cilexetil alone, and 0.8% with candesartan cilexetil as add-on therapy. Thus, candesartan cilexetil either alone or as add-on therapy was highly effective for the control of systolic or diastolic hypertension regardless of demographic background when used in typical clinical practice settings. Am J Hypertens 2001; 14:567–572 © 2001 American Journal of Hypertension, Ltd.

Key Words: Candesartan cilexetil, angiotensin receptor blocker, add-on antihypertensive therapy.
success rates of blood pressure control in various clinical trials. It is now recognized that results from small controlled studies may not reflect actual clinical practice. In general, a single antihypertensive agent provides adequate control for only 50% of hypertensive patients. The recent Hypertension Optimal Treatment (HOT) Trial not only confirms that intensive BP control to diastolic blood pressure (DBP) <90 mm Hg improves outcomes but also that multiple agents are required to achieve this goal.

The renin-angiotensin system (RAS) plays an important role in the pathophysiology of hypertension. Angiotensin II receptor blockers (ARB) provide specific blockade of the RAS by blocking the action of angiotensin II directly at the AT1 receptor. Candesartan is a highly selective, insurmountable AT1 subtype angiotensin II receptor antagonist devoid of agonist activity. Controlled studies have demonstrated a sustained dose-related antihypertensive effect throughout the 24-h dosing interval with a high trough-to-peak ratio, and most effective BP reduction with doses of 16 to 32 mg once daily in a diverse population of US patients.

A large-scale open-label clinical experience trial (ACTION study) was performed to evaluate the effectiveness of candesartan cilexetil either alone or with other agents in patients with essential hypertension (HBP) or isolated systolic hypertension. The present report summarized the findings of its use as add-on therapy, whereas the BP-lowering effects of candesartan cilexetil specifically in patients with HBP or ISH were reported separately.

**Methods**

This 8-week, multicenter, open-labeled, single-arm study evaluated the use of candesartan cilexetil in 6465 patients with essential hypertension or isolated systolic hypertension at 665 investigative sites. The subjects included men and women without childbearing potential ≥18 years of age, with either untreated or uncontrolled hypertension (sitting systolic BP [SBP] in the range of 140 to 179 mm Hg or a DBP of 90 to 109 mm Hg inclusive at baseline). Patients were given candesartan cilexetil (16 mg once daily) either alone or as add-on therapy to concomitant antihypertensive medications (background therapy) at the discretion of the investigators. Background therapy with any one or more agents was permitted except for concomitant use of another ARB. Patients returned for study visits after 2, 4, and 8 weeks of treatment. If BP remained uncontrolled (DBP ≥90 mm Hg or SBP ≥140 mm Hg) at either week 2 or 4, candesartan cilexetil was to be increased to 32 mg once daily and treatment was continued for a total treatment period of 8 weeks. Decreases in study drug dose or changes in background therapy were not permitted.

In general, the numbers of patients tallied for different assessments in the groups do not always add to the total because of occasional missing data and differ because of the intent-to-treat approach.

### Results

The ACTION study included a diverse population of US patients (n = 6465) that was 52% female, 16% African American, and 34% ≥65 years old, with a mean age of 58 years (Table 1). The efficacy results are presented separately for HBP and ISH. A total of 51% patients with HBP and 66% patients with ISH received candesartan cilexetil as add-on therapy. The background therapy included, in order of frequency, diuretics, calcium antagonists, β-blockers, angiotensin converting enzyme (ACE) inhibitors, and α-blockers either singly or in combination.

Of the 5446 patients with HBP, 5156 patients provided information with the use of candesartan cilexetil either
alone or as add-on therapy; 2642 (51%) patients received candesartan cilexetil as add-on therapy and 2514 (49%) received candesartan cilexetil as monotherapy. The use of candesartan cilexetil led to an overall control rate (DBP, 90 mm Hg) of 71%. Fig. 1 shows the BP-lowering efficacy of candesartan cilexetil as monotherapy and as add-on therapy to major classes of background therapy. Candesartan cilexetil, as monotherapy, reduced SBP/DBP by 18.7/13.1 mm Hg. As add-on therapy, candesartan cilexetil 16 to 32 mg once daily reduced SBP/DBP by 17.8/11.7 mm Hg in 1066 patients with a diuretic, 16.6/11.2 mm Hg in 1065 patients with a calcium antagonist, 16.5/10.4 mm Hg in 755 patients with a β-blocker, 15.3/10.0 mm Hg in 473 patients with an ACE inhibitor, and 16.4/10.4 mm Hg in 249 patients with an α-blocker. All these changes were statistically significant.

Changes in trough sitting SBP and DBP were similar for male and female patients with HBP receiving candesartan cilexetil with or without background therapy. Likewise, neither age (<65 and ≥65 years of age) nor race (African American and non-African American) interfered with the improved BP when adding the ARB to the background therapy. Effective additional BP reduction was consistently observed in each of the predefined groups: men and women, African Americans and non-African Americans, age <65 years and age ≥65 years. In general, African Americans had a clinically important but somewhat lesser further BP reduction than non-African Americans.

Of the 1014 patients with ISH, 964 patients provided information with the use of candesartan cilexetil either alone or as add-on therapy; 634 patients (66%) received candesartan cilexetil as add-on therapy and 330 patients (34%) received candesartan cilexetil as monotherapy. The mean baseline BP was 158/81 mm Hg. The use of candesartan cilexetil as add-on and monotherapy led to an overall control rate (SBP <140 mm Hg) of 49%. Figure 2 shows the BP-lowering efficacy of candesartan cilexetil as monotherapy and as add-on therapy to major classes of background therapy. Candesartan cilexetil, as monotherapy, lowered SBP/DBP by 17.0/4.4 mm Hg. As add-on therapy, candesartan cilexetil 16 to 32 mg once daily reduced SBP/DBP by 17.4/5.1 mm Hg in 278 patients with a diuretic, 15.6/3.6 mm Hg in 277 patients with a calcium antagonist, 14.0/4.8 mm Hg in 197 patients with a β-blocker, 13.4/4.3 mm Hg in 127 patients with an ACE inhibitor, and 11.6/4.5 mm Hg in 65 patients with an α-blocker. These changes were statistically significant.

As with the patients with HBP, patients with ISH demonstrated effective additional SBP reduction with candesartan cilexetil as add-on therapy in each of the predefined groups: men and women, African American and non-African American patients, age <65 years and age ≥65 years.
American patients had a clinically important but somewhat lesser SBP reduction than non-African American patients, and women had a somewhat greater reduction than men with some treatment combinations.

Overall, 6.8% of all patients withdrew from the trial due to adverse effects, most commonly headache (6.3%) and dizziness (5.0%). Orthostatic hypotension was infrequent, 0.2% with candesartan cilexetil as monotherapy and 0.8% with candesartan cilexetil as add-on therapy.

**Discussion**

This large-scale clinical experience trial confirms the efficacy of the ARB candesartan cilexetil as an antihypertensive agent for treating diastolic and systolic hypertension in a diverse US population in typical clinical practice settings. Importantly, the present study demonstrates that this ARB is highly effective in further BP reduction when used as add-on therapy with a wide variety of commonly prescribed antihypertensive drugs. In general, African Americans had a slightly lesser BP reduction than non-African Americans, but the magnitude of the BP reduction was substantial and clinically meaningful.

The findings of the present study are strikingly similar to those of another large-scale experience trial (Atacand Under Real-Life Aspects [AURA]) with candesartan cilexetil either as monotherapy or add-on therapy, conducted contemporaneously in Germany. In 4531 patients with HBP, candesartan cilexetil 8 to 32 mg once daily as monotherapy (n = 1867) reduced DBP by 17.8 mm Hg, whereas a further mean DBP reduction of 14.9 mm Hg was reported when used as add-on therapy with ACE inhibitors (n = 235), 16.3 mm Hg with β-blockers (n = 477), 15.0 mm Hg with calcium antagonists (n = 434), and 14.9 mm Hg with other combinations (n = 1475).

There are sound theoretical bases for expecting a high level of effectiveness with an ARB as an add-on therapy. For instance, the additional BP-lowering efficacy of an ARB with an ACE inhibitor is explained by their different and perhaps, complementary effects in antagonizing the RAS. It is well-known that plasma levels of angiotensin II do not remain low persistently but instead return toward baseline values with chronic ACE inhibitor therapy. This may be related to alternate synthetic pathways for angiotensin II production that are not affected by ACE inhibitors. Thus, during the longer term, ACE inhibitors do not antagonize the RAS completely and the addition of an ARB could provide increased effect. Alternatively, some experimental studies suggest that an ARB may increase tissue bradykinin production by shifting angiotensin II binding to the AT2 receptor. Thus, inhibition of bradykinin breakdown with an ACE inhibitor could augment the effect of the ARB on tissue bradykinin production. The findings of a study (Candesartan Lisinopril Microalbuminuria [CALMI]) in diabetic hypertensive patients that the combination of candesartan cilexetil 16 mg and lisinopril 20 mg lowered the BP by 25.5/16.3 mm Hg and was
Candesartan cilexetil 16 mg to 32 mg once daily is highly effective as monotherapy or as add-on therapy in patients with HBP or ISH. Substantial further BP reductions with excellent tolerability can be achieved with the addition of candesartan cilexetil to a variety of regimens across a diverse population of US patients.

Acknowledgments

We gratefully acknowledge the diligent efforts of the clinical study investigators at the 665 investigative sites. A list of investigators is available on request. We also recognize the contributions of Susan Harris, MS, Diane Edwards, BA, Michaelene Llewellyn, MAS, Emmanuel Bravo, MD, Terry Flanagan MPH, Denise Hardison, MS, Larrye Loss, PharmD, Robert Lamb, PharmD, James Gaddy, PhD, Oliver Yeh, BA, Debbie Brangman, MBA, Jeanne Holeman, MBA, and Steve Cullinan, MBA for invaluable assistance in the conduct of the study and manuscript preparation.

References


