

Candesartan

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ABSTRACT

Candesartan cilexetil is the prodrug of candesartan, an angiotensin II receptor antagonist. Candesartan binds selectively and non-competitively to the angiotensin II receptor type 1, thus preventing the actions of angiotensin II. Clinical trials have demonstrated its efficacy at a dose range of 2 to 32 mg once daily in hypertension of all grades, heart failure, in reducing urinary albumin excretion in diabetes mellitus and in coexisting hypertension and renal failure.

Pharmacokinetic properties of candesartan cilexetil in elderly patients are not significantly different from those in younger individuals. Hepatic impairment does not change pharmacokinetics of candesartan cilexetil at doses up to 12 mg/day. No dose adjustment is necessary in patients with mild or moderate renal impairment.

Tolerability of candesartan cilexetil is not much different from that of placebo. All adverse events are usually of mild to moderate severity and not dose-related. The most common adverse events were headache, upper respiratory tract infection, back pain, and dizziness. The incidence of these adverse effects, as well as of cough, was similar in patients treated with candesartan cilexetil or placebo. The incidence of adverse events in long-term trials was not different from that in short-term trials. Tolerability of candesartan cilexetil does not differ with either age or gender.

INTRODUCTION

Angiotensin II receptor antagonists have been thought to provide potential advantages over angiotensin converting enzyme inhibitors (ACEIs; e.g. captopril or enalapril). One of the advantages is their high specificity in blocking the effects of circulating and tissue angiotensin II at the AT₁ receptor level (56). ACEIs prevent the enzymatic cleavage of angiotensin I and thus the formation of angiotensin II. They have been proven to be effective in the treatment of hypertension or heart failure. However, in addition to blocking renin-angiotensin system ACEIs increase the levels of other substrates of ACE, including bradykinin (90) that produces dry cough. Thus, AT₁ receptor antagonists can be used to replace ACEIs in patients who do not tolerate them and suffer from cough or angioedema.

Like most AT₁ receptor antagonists, candesartan cilexetil is approved in many countries for the treatment of hypertension only (55). Its use in heart failure is currently under investigation (76). Similarly to the AT₁ receptor antagonists, e.g. losartan or valsartan (77), candesartan cilexetil has not been yet unequivocally shown to be superior to ACEIs in the therapy of heart failure (58,84,76).

In patients with non-insulin dependent diabetes, candesartan cilexetil is not more effective in lowering blood pressure and reducing microalbuminuria than the ACEI, lisinopril. Dual blockade of renin-angiotensin system with candesartan cilexetil and lisinopril appears to be more effective in reducing blood pressure than either drug alone, but uncertainties in the clinical endpoints have not yet been clarified (63).

CHEMISTRY

Candesartan cilexetil (Fig. 1) has been developed in a program of Takeda Chemical Industries Ltd. with the aim of identifying a non-peptide angiotensin II receptor antagonist with a long-lasting and insurmountable effect. Studies with benzimidazole carboxylic acid derivatives showed that three important structural features on the benzimidazole ring were associated with potent angiotensin II receptor antagonism: a tetrazolyl moiety, a lipophilic side chain, and a carboxyl group. The introduction of a carboxyl group at the seven-position of the benzimidazole ring provided angiotensin II receptor blocking properties that had been searched for (69).

Since candesartan is poorly absorbed by oral administration, ester prodrugs were synthesized. One of them, candesartan cilexetil (TCV-116), a non-peptide esterified prodrug of candesartan with the strongest oral angiotensin II (Ang II) type 1 (AT₁) receptor antagonistic activity, has been selected from the series of ester prodrugs (69). Candesartan cilexetil is a white crystalline powder with a molecular weight of 610. It is highly soluble in dimethylsulfoxide or 1N sodium carbonate solution; it is only sparingly soluble in methanol, ethanol, water or physiological saline solution. The therapeutic effect of candesartan cilexetil depends solely upon generation of the active metabolite, candesartan (CV-11974; Fig. 1). The prodrug is rapidly and completely converted to candesartan during gastrointestinal absorption. In all *in vivo* studies reviewed in this article, including clinical trials, candesartan cilexetil was used, so that all doses refer to candesartan cilexetil in mg.

Candesartan is a white crystalline powder with a molecular weight of 440, it contains two acidic functional groups: a carboxyl and a tetrazole moieties ($pK_a = 5.3$ for either). Candesartan is slightly soluble in water and physiological saline and soluble in 1 N sodium carbonate solution (69).

PHARMACOLOGY

The AT₁ receptor

The angiotensin-converting enzyme (ACE) converts the inactive decapeptide angiotensin I to angiotensin II. The discovery of specific angiotensin II receptor antagonists led to the identification of various subtypes of angiotensin II receptors (98). Candesartan selectively inhibits angiotensin II type 1 (AT₁) receptors. In rodents, AT₁ receptors have been further subdivided into AT_{1A} and AT_{1B} receptors. AT₁ receptors, like AT₂ receptors, belong to the superfamily of G-protein-coupled receptors (14).

AT₁ receptors have been localized in vascular smooth muscles, kidney, heart, brain, adrenal gland, platelets, adipocytes, and placenta. All the known clinical effects of angiotensin II are mediated by the AT₁ receptor. Among these effects are vasoconstriction, increase in sodium retention, suppression of renin secretion, increase of endothelin secretion, increase of vasopressin release, activation of sympathetic activity, promotion of myocyte hypertrophy, stimulation of vascular and cardiac fibrosis, increase of myocardial contractility, and induction of arrhythmia (14).

As a potent AT₁ receptor antagonist, candesartan is a suitable pharmacological tool to study renin-angiotensin system *in-vitro* or *in vivo*.

In vitro studies

Candesartan binds to the angiotensin II receptor subtype 1 (AT₁ receptor). In contrast, candesartan does not affect angiotensin II activity at the angiotensin II receptor subtype 2 (AT₂ receptor). Candesartan specifically binds to the AT₁ receptor in a monophasic and

concentration-dependent fashion. Candesartan dissociates from bovine AT₁ receptors about 5 times more slowly than angiotensin II (66 vs 12 min) (74).

Candesartan is a potent AT₁ receptor antagonist. In an *in vitro* study using an AT₁ receptor expression system and comparing the inhibition of the AT₁ receptor by AT₁ receptor antagonists, candesartan was shown to have a higher potency (lower IC₅₀) than eprosartan, irbesartan, valsartan, or the active metabolite of losartan [EXP-3174, 2-n-butyl-4-chloro-1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)imidazole-5-carboxylic acid] (43). Binding of candesartan to the AT₁ receptor was shown to be non-competitive (92). AT₁ binding affinity of candesartan in the rabbit aorta is 80 times higher than that of losartan and 10 times higher than that of EXP-3174 (14).

In vitro preincubation of isolated vascular tissue with candesartan reduces the maximal contractile response to angiotensin II (non-competitive antagonism). Non-competitive blockade is characterized *in vitro* by a nonparallel displacement of the angiotensin II dose-response curves, i.e. increasing doses of angiotensin II cannot completely displace candesartan from its receptor sites. In contrast, losartan causes a parallel shift to the right of the angiotensin II dose-response curve without diminishing the maximal effect (competitive antagonism) (69).

The kinetics of candesartan metabolism by cytochrome P450 isoforms: CYP2C9*1/*1 and CYP2C9*1/*3, in human liver microsomes did not differ significantly. It has been studied in a yeast expression system of CYP2C9*1 and CYP2C9*3: The wild-type showed the lower K_m (345 vs 439 microM; 3/4) and higher V_{max}/K_m (1/3) than the *3 variant. Experiments with S-warfarin 7-hydroxylation suggested that CYP2C9*3, unlike CYP2C9*1, may change not only the metabolic activity but also the inhibitory susceptibility (36).

***In vivo* animal studies**

Candesartan has been reported to cross blood-brain barrier in rats (70). It remains to be shown, however, whether AT₁ receptor blockade by candesartan in the brain of hypertensive patients contributes to its antihypertensive efficacy by suppressing central control of sodium uptake, thirst and sympathetic activity.

In several animal models of hypertension, candesartan had a marked and long-lasting effect. For example, following oral administration to rats, candesartan cilexetil 0.3 mg/kg completely inhibited the angiotensin II-induced pressor response for 7 to more than 24 h. Based on the doses producing 50% inhibition of the angiotensin-II-induced pressor response candesartan cilexetil was approximately 40 times more potent than losartan. However, it had no effect on the bradykinin-induced depressor response in the rat, while enalapril potentiated this effect of bradykinin (69).

Candesartan cilexetil, 10 mg/kg, had little effect on blood pressure in a renin-angiotensin system independent model, DOCA/salt hypertensive or normotensive rats, in which renin-angiotensin system has not been overly activated (69).

Candesartan may attenuate sympathetic tone by inhibiting presynaptic AT₁ receptors. This assumption is based on the observation that in isolated perfused mesenteric vasculature of spontaneously hypertensive rats (SHR), candesartan cilexetil inhibited the release of norepinephrine induced by electrical stimulation of periarterial adrenergic nerves. In the rat, candesartan cilexetil markedly reduced plasma aldosterone levels elevated by intravenous infusion of angiotensin II. In SHR, candesartan cilexetil caused a dose-dependent increase in plasma renin and a reduction in plasma aldosterone levels (103). Inhibition of aldosterone production is thought to contribute to the antihypertensive effect of candesartan cilexetil in SHR.

Independent of blood pressure reduction, candesartan cilexetil prevented or reduced left ventricular hypertrophy in animal models. In one study candesartan-treated SHR were compared with those of age-matched untreated controls. Candesartan significantly reduced left ventricular weight and size, diameter of cardiac myocytes, incidence of cardiac fibrosis and total coronary vascular resistance (55). In stroke-prone SHR candesartan cilexetil, at 1 mg/kg/d, reduced proteinuria (67).

In animal models of myocardial infarction or intimal hyperplasia, candesartan cilexetil reduced cardiovascular damage after infarct or injury. In SHR pre-treatment with candesartan cilexetil reduced volume of ischemic brain injury caused by from temporary occlusion of middle cerebral artery (71). The drug also reduced the incidence of stroke in stroke-prone SHR (42).

By intrajugular administration candesartan abolished angiotensin II-induced PAI-1 expression in rat aorta and ventricles. It had, however, no effect on increased PAI-1 expression in rats with inhibited nitric oxide (NO) synthesis (23).

In a rat model with spontaneous diabetes mellitus, candesartan preserved left ventricular diastolic function (38).

A recent study in the rat tested the hypothesis that AT₁ receptor blockade by candesartan improves β -adrenoceptor responsiveness in heart failure after myocardial infarction by uncoupling β -adrenoceptors through cross-talk between angiotensin and β -adrenoceptor signaling. Treatment with candesartan during the chronic phase of myocardial infarction improved β -adrenoceptor coupling in noninfarcted myocardium without basal left ventricular function. Cross-talk between β -adrenoceptor and angiotensin signaling through β -adrenoceptor kinase-1 and protein kinase C-epsilon may be responsible for this phenomenon (95).

TOXICOLOGY

In mice, rats or dogs candesartan cilexetil, at single oral doses up to 2000 mg/kg, caused no death. In a 4-week-long toxicity in rats and dogs candesartan cilexetil, at high doses increased plasma urea nitrogen and decreased erythrocyte count and heart weight. On histopathologic examination, hypertrophy of the renal juxtaglomerular cells and of basophilic renal tubular epithelium was noted. Also, atrophy of the adrenal zona glomerulosa cells was observed (69).

Candesartan cilexetil had no adverse effects on fertility of rats. No teratogenic effects were seen in rats, rabbits, or mice. Upon administration to female rats, from the late period of gestation to weaning, hydronephrosis in the offspring's kidneys has been observed. Similar effects have been reported for an angiotensin-converting enzyme (ACE) inhibitor, trandolapril, and another angiotensin II antagonist, losartan (69).

Gene mutation, chromosome aberration and DNA damage tests or long-term carcinogenicity studies in rats and mice showed no mutagenic or oncogenic potential (69).

PHARMACOKINETICS

Oral bioavailability of candesartan cilexetil is low (about 40%) due to incomplete absorption. Absorbed candesartan cilexetil is completely metabolized to candesartan. Plasma protein binding in humans is >99%. The volume of distribution in healthy subjects is 0.13 L/kg. After reaching systemic circulation candesartan is cleared mainly by kidneys and to a smaller extent by biliary or intestinal routes (32). A comparison of its pharmacokinetic profile with those of other marketed AT₁ receptor antagonists is presented in Table 1. In healthy

subjects the apparent oral clearance of a single dose of candesartan cilexetil is 0.25 L/h/kg. Oral clearance is highly variable in patients (3.4 to 28.4 L/h). No relevant pharmacokinetic drug-food or drug-drug interactions between candesartan and nifedipine, glibenclamide (glyburide), digoxin, ethinylestradiol/levonorgestrel, warfarin, or hydrochlorothiazide are known (32). As with ACE inhibitors, coadministration of candesartan cilexetil and lithium may result in a reversible increase in serum lithium concentration. Monitoring of serum lithium levels is, therefore, recommended (3). Until recently no known clinically relevant cytochrome P450 interactions with candesartan have been reported (32). A marked hypotensive effect of candesartan cilexetil in a single patient with hypertension and heart failure has been recently reported by Uchida et al. (101) polymorphism analysis revealed heterozygous poor metabolizer genotype CYP 2C9*1/*3. Oral clearance of candesartan cilexetil in this patient was 48% lower than that in the average elderly population. Reduced CYP2C9 activity associated with the CYP2C9*1/*3 genotype may be clinically meaningful in patients receiving candesartan cilexetil. Four percent of Japanese and 10% of Caucasians are known to express this heterozygous genotype.

Terminal elimination half-life of candesartan cilexetil remains unclear, but it appears to be longer than the currently estimated range of 4 to 9 h. Non-compartmental models do not appear to be appropriate for the analysis of candesartan pharmacokinetics. In hypertensive patients a two-compartment analysis revealed a much longer half-life of 29 h. A further in-depth analysis never has taken place up-to-date. The concentration-effect relationship of candesartan is unaffected by age. It appears that neither pharmacokinetics nor efficacy of candesartan are affected by gender or race (32).

Renal function affects the pharmacokinetics of candesartan cilexetil. In patients with creatinine clearances of $>60 \text{ mL}/(\text{min}\cdot 1.73\text{m}^2)$, $30\text{-}60 \text{ mL}/(\text{min}\cdot 1.73\text{m}^2)$, and $15\text{-}30 \text{ mL}/(\text{min}\cdot 1.73\text{m}^2)$, elimination half-life of candesartan cilexetil, 8 mg/d was 7.1, 10.0, and

15.7 h, respectively. At 12 mg/d, however, the accumulation factor was 1.71. Thus, a maximum daily dose of up to 8 mg appears suitable for patients with severe renal dysfunction. During hemodialysis there was no significant elimination of candesartan. Mild to moderate hepatic impairment does not seem to affect pharmacokinetics of candesartan. In patients with mild to moderate liver disease up to 12 mg candesartan cilexetil can be administered without any dose adjustment. From a pharmacokinetic point of view, candesartan appears to be a comparatively easy-to-handle drug. Because of lack of data, candesartan is not recommended for pregnant or breast-feeding women and should not be used in children (32).

CLINICAL PHARMACODYNAMICS

An attenuated response to exogenous angiotensin II has been demonstrated in various double-blind, randomized, crossover trials with candesartan cilexetil in healthy male volunteers. Approximately 25 to 30 times the amount of angiotensin II was required to achieve the same diastolic blood pressure increase after treatment with a therapeutic oral dose of candesartan cilexetil (4 to 16 mg) (23).

Clinically effective doses of candesartan cilexetil range between 8 and 32 mg/d. The response rate to monotherapy of hypertension with candesartan cilexetil increases with dose but never exceeds 60% at a daily dose of 16 mg. Even at doses up to 32 mg/day this response rate was not further increased (32).

The pharmacodynamics and pharmacokinetics of various AT₁ receptor antagonists are rather similar. The drugs differ primarily in their routes of elimination. No systematic attempts have been made to compare the clinical effects and doses of various AT₁ receptor antagonists. Comparison of irbesartan (150 mg) and candesartan cilexetil (8 mg)

demonstrated a similar extent and duration of the blockade of the pressor effects of angiotensin II. Irbesartan appeared to show a higher antagonistic activity in plasma as demonstrated by higher plasma renin activity and stronger reduction in aldosterone levels (10). The antihypertensive effect of candesartan cilexetil doubled with the increase in the dose from 4 to 16 mg/day (25). Dose-response relationships for different AT₁ receptor blockers in patients with hypertension show the greatest reduction in trough diastolic blood pressure for candesartan cilexetil [at the highest doses almost 2 mmHg more lowering in trough diastolic pressure than with either losartan, valsartan, or irbesartan (37)]. Dominiak and Häuser (22) found the following “equivalent” doses for the reduction of sitting blood pressure by 8 to 10 mmHg: losartan, 100 mg = valsartan, 160 mg = irbesartan, 150 mg = telmisartan, 40 mg = olmesartan, 20 mg = candesartan, 16 mg = eprosartan, 800 mg.

Angiotensin II caused a dose-dependent increase in the expression of plasminogen-activator inhibitor-1 (PAI-1), the major physiological inhibitor of fibrinolysis *in vivo*. Candesartan abolished angiotensin II-induced PAI-1 expression *in vitro* and in animal studies but increased it in postmenopausal women (23). A recent paper addressing this question in healthy normotensive subjects found that there was an interactive effect of endogenous angiotensin II and aldosterone on PAI-1 production in humans and that candesartan together with spironolactone was able to reduce furosemide-induced increase in PAI-1 levels (85).

In patients with coronary artery disease (CAD) candesartan cilexetil improved flow-dependent, endothelium-mediated vasodilation. This effect was inhibited by either icatibant, a bradykinin B₂-receptor antagonist, or by N-monomethyl-L-arginine (L-NMMA), an NO synthase inhibitor, suggesting that both bradykinin and NO contributed to the vascular effects of candesartan in this patient population (41). Accordingly, in CAD patients with a history of coronary intervention, candesartan cilexetil, at a low dose (4 mg/d), which did not alter blood pressure levels, appeared to reduce cardiovascular risk (46).

In normal individuals candesartan cilexetil (4 to 16 mg orally) attenuated the response to exogenous angiotensin II. It significantly increased plasma renin activity and plasma angiotensin II levels. In contrast to patients with hypertension, a significant reduction of aldosterone plasma levels has not been observed. Cardiac output, heart rate or stroke volume were not altered by candesartan cilexetil, but renal blood flow was increased in a dose-dependent fashion.

In healthy male volunteers, candesartan cilexetil produced a rightward shift of the angiotensin II dose-response curve (11). Candesartan cilexetil (8 mg/d) and losartan (50 mg/d) for 7 days appeared to produce different pharmacodynamic effects as assessed by the rightward shift of the angiotensin II dose-response curve. In healthy volunteers the angiotensin II antagonistic effect of candesartan cilexetil was longer-lasting than that of losartan (31).

In a double-blind, randomized crossover study in healthy men, irbesartan 150 mg and candesartan cilexetil 8 mg exerted similar substantial (>30-fold) and long-lasting (>2-fold at 47 h after treatment) rightward shift of the angiotensin II dose-response curve. This effect declined with a half-life of 15 and 12 h, for irbesartan and candesartan, respectively. Both drugs increased plasma renin activity, decreased diastolic blood pressure, and suppressed aldosterone (12).

By chronic administration to healthy volunteers candesartan cilexetil, 16 mg once daily for two weeks, effectively suppressed pressor responses to angiotensin II. At 2 hours after the last dose, forearm blood flow responses to norepinephrine were suppressed, while blood pressure responses to intravenous norepinephrine were unaltered (99). In elderly women candesartan cilexetil, 8-16 mg once daily for 3 weeks, unmasked a vasodilator response to infused angiotensin II. Angiotensin II type 2 (AT₂) receptor blockade with PD

123319 infusion increased forearm vascular resistance in these patients. This blockade did not prevent vasodilator responses to angiotensin II, suggesting that vasodilator mechanisms, other than activation of AT₂ receptors, may have been involved (79).

CLINICAL STUDIES

Hypertension

The use of candesartan cilexetil in essential hypertension has been reviewed extensively (23).

Candesartan cilexetil induced a dose-dependent reduction in the diastolic blood pressure response to angiotensin II. It significantly increased plasma renin activity and plasma angiotensin II level. In patients with hypertension, but not in healthy normotensive individuals, candesartan cilexetil significantly reduced plasma aldosterone levels (28). Plasma catecholamine levels were not affected by candesartan cilexetil.

In patients with hypertension, candesartan cilexetil significantly reduced diastolic, systolic and, mean arterial pressures, total systemic and forearm vascular resistance, but had no effect on cardiac output, heart rate or stroke volume in patients with hypertension or healthy volunteers (23). In hypertensive patients it reduced endothelial dysfunction by restoring tonic NO release and blunting the vasoconstrictor response to endogenous endothelin-1 (23).

As demonstrated in three trials on a total of 127 hypertensive patients candesartan cilexetil, reduced blood pressure and left ventricular mass index (LVMI). Reversal of left ventricular hypertrophy may be more strongly related to changes in the renin-angiotensin-aldosterone system than to reduction in blood pressure per se (18).

The height of pulse pressure, i.e. the difference between systolic and diastolic blood pressure, is considered an independent cardiovascular risk factor. In the CHAMP Study (Candesartan cilexetil in *Hypertension Ambulatory Measurement of Blood Pressure*), in patients with mild to moderate hypertension, candesartan cilexetil, 8 mg once daily, decreased ambulatory pulse pressure significantly more than losartan, 50 mg once daily, and its effect was more sustained (4).

In a randomized, double-blind, placebo-controlled crossover study in patients with primary hypertension candesartan cilexetil, 16 mg, once daily for 6 weeks, reduced renal vascular resistance and tended to increase renal plasma flow despite a reduction in mean arterial pressure (29).

In patients with moderate-to-severe hypertension, candesartan cilexetil, 8 to 16 mg once daily, effectively lowered blood pressure alone, in combination with amlodipine, 5 mg once daily, or with amlodipine plus hydrochlorothiazide, 25 mg once daily (50).

In a randomized double-blind, parallel-group trial, hypertensive women were better controlled with candesartan cilexetil, 8 to 16 mg, than with enalapril, 10 to 20 mg, or hydrochlorothiazide, 12.5 to 25 mg, as assessed by the proportions of patients with controlled diastolic pressure (<90 mm Hg; 60%, 51%, 43% respectively). In addition, patients experienced less dry cough with candesartan cilexetil or hydrochlorothiazide than with enalapril. Incidence of dizziness and quality of life were not different with any of the three drugs(51).

In a double-blind, randomized, parallel group study losartan, 50 mg once daily, possibly titrated to 100 mg, and candesartan cilexetil 8 mg once daily, possibly titrated to 16 mg, were comparable in terms of blood pressure reduction. After titration, however, losartan 50 mg plus hydrochlorothiazide 12.5 mg was superior to either candesartan cilexetil 16 mg or

losartan 100 mg. Losartan, but not candesartan cilexetil, lowered serum uric acid levels and attenuated the expected increase in uric acid levels with hydrochlorothiazide, 12.5 mg (52).

In a double-blind randomized parallel group trial candesartan cilexetil, 8 mg once daily or lisinopril 10 mg once daily, each in a fixed combination with hydrochlorothiazide, 12.5 mg once daily, were equally effective antihypertensive agents. The fixed combination containing candesartan cilexetil was better tolerated than that containing lisinopril. The proportion of patients spontaneously reporting cough (4.6 vs. 23.1%) or discontinuing therapy due to adverse events (5.9 vs. 12.0%) was lower in the candesartan cilexetil than in the lisinopril group (57).

The reduction in blood pressure and the proportion of patients with normalized blood pressure was greater with a candesartan cilexetil 16 mg plus hydrochlorothiazide 12.5 mg combination than with losartan 50 mg plus hydrochlorothiazide 12.5 mg. This was the main finding of a randomized controlled trial in patients with mild-to-moderate primary hypertension (73).

In hypertensive patients with confirmed enalapril-induced cough, the incidence (35.5% vs. 68.2%) frequency and severity of dry cough was significantly lower with candesartan cilexetil than with enalapril and not different from that found with placebo (97).

In a multicenter, double-blind, randomized, parallel-group, forced-titration study (Antihypertensive efficacy of candesartan in comparison to losartan: The CLAIM Study), candesartan cilexetil, 16 mg once daily, was more effective than losartan 50 mg once daily (5). In the CLAIM II study candesartan cilexetil was more effective in lowering blood pressure than losartan when compared at once daily maximal doses (candesartan cilexetil 32 mg and losartan 100 mg) (102).

In a double-blind and randomized SWITCH trial (complete study title: Change from ACE-inhibitor, Ca-antagonist or beta-blocker to candesartan cilexetil: better efficacy and tolerance) ambulatory hypertensive patients, who were inadequately controlled by or did not tolerate ACE inhibitors, beta-blockers or calcium channel blockers have been safely and effectively switched to monotherapy with candesartan cilexetil 8 or 16 mg (7).

In a double-blind, placebo-controlled, randomized, parallel-group trial, patients with mild to moderate primary hypertension, who did not reach target blood pressure with candesartan cilexetil, 16 mg, were switched to a fixed combination of candesartan cilexetil 16 mg and hydrochlorothiazide 12.5 mg once daily. This combination therapy reduced their sitting diastolic blood pressure significantly better than candesartan cilexetil 16 mg combined with placebo (15).

The change in mean diastolic and systolic ambulatory blood pressure at 22 to 24 hours after treatment was the primary efficacy variable in a randomized clinical trial in patients with mild to moderate hypertension. This trial compared the efficacy of candesartan cilexetil, 8 to 16 mg once daily, with that of enalapril, 10 to 20 mg once daily, with forced dose titration after 4 weeks. Non-invasive ambulatory blood pressure measurements were taken for 36 hours at the baseline and again after 8 weeks. Candesartan cilexetil, 16 mg, was found to lower blood pressure more effectively than enalapril, 20 mg, at trough and particularly on the day following the last treatment day (39).

In a double-blind randomized, parallel-group, forced-titration trial in patients with mild hypertension candesartan cilexetil 16 mg once daily, titrated up to 32 mg, was associated with a significantly lower occurrence of peripheral edema (8.9%; mild 8.1%, moderate 0.8%) than amlodipine 5 mg once daily, titrated up to 10 mg, (22.1%; mild 8.7%, moderate 11.8%, severe 1.6%) (44).

In a multicenter, double-blind, randomized, parallel-group 24 weeks-long trial in elderly hypertensive patients (≥ 75 years) candesartan cilexetil, 8 mg, was compared with hydrochlorothiazide, 12.5 mg. Candesartan cilexetil was well tolerated. Hydrochlorothiazide (but not candesartan) produced hypokalemia (8.1%) and hyperuricemia (6.5%) (68).

A randomized, double-blind, two-way crossover study in patients with essential hypertension was designed to evaluate intraindividual variability in the blood pressure responses to candesartan cilexetil and lisinopril. A marked heterogeneity in the responses to the two drugs was found. Fifty percent of patients responded to either drug, 16% were non-responders to either drug, 20% responded to lisinopril but not to candesartan, while 15% responded to candesartan but not to lisinopril (89).

Candesartan cilexetil (4 mg, increased to 8 mg in non-responders), enalapril (10 mg, increased to 20 mg in non-responders), and placebo, were compared in a randomized, double-blind, parallel-group trial in patients with mild to moderate hypertension. Both active treatments reduced blood pressure similarly and were significantly more effective than placebo (105).

Candesartan cilexetil, 16 mg once daily, reduced resting blood pressure in patients with essential hypertension significantly better than losartan, 50 mg once daily, or valsartan 80 mg once daily. In this randomized controlled trial, candesartan cilexetil almost completely inhibited the renal vasoconstriction induced by exogenous angiotensin II (30).

The antihypertensive effect of felodipine, a dihydropyridine calcium channel blocking drug, was additive to that of candesartan (64).

Genotypes of the CYP11B2 promotor polymorphism can predict a positive response to candesartan. This finding was made in a prospective trial in patients with diastolic

hypertension receiving candesartan cilexetil (8 or 16 mg) in addition to the standard medication (75).

In a randomized, open-label, parallel-group, multicenter trial, involving 968 patients with mild to moderate essential hypertension, candesartan was found to be a safe and effective alternative to other antihypertensive drugs. The patients in this trial were previously treated with, but developed adverse reactions to ACE inhibitors, beta-blockers, calcium channel blockers or thiazide diuretics (82).

As shown in the CATCH (Candesartan Assessment in the *Treatment of Cardiac Hypertrophy*) study, a prospective randomized double-blind trial in 239 patients with hypertension, candesartan cilexetil, 8 to 16 mg once daily, reduced echocardiographic left ventricular mass index (LVMI) to the same extent as enalapril (10 to 20 mg once daily) with or without addition of hydrochlorothiazide (17).

In a Japanese prospective crossover study in 73 essential hypertensive patients candesartan or lisinopril had almost identical effects on 24-hour blood pressure, with candesartan being superior in decreasing morning blood pressure and morning blood pressure surge (24).

The Swedish ALPINE (Antihypertensive Treatment and *Lipid Profile in a North of Sweden Efficacy Evaluation*) study, a 1-year, prospective randomized, double-blind, controlled trial in 392 patients with newly diagnosed primary hypertension compared long-term effect of low-dose hydrochlorothiazide, alone or in combination with atenolol, with that of candesartan, alone or in combination with felodipine. A less favorable metabolic profile (increase of triglycerides and decrease of HDL-cholesterol) was found in the hydrochlorothiazide + atenolol than in the candesartan + felodipine group, and significantly

($P = 0.007$) more patients in the former (18) than in the latter group (5) developed metabolic syndrome at 12 months (48).

In the *Candesartan and Lisinopril Microalbuminuria (CALM)* study, a prospective, randomized, parallel-group, double-blind trial, candesartan cilexetil, 16 mg once daily, was as effective as lisinopril, 20 mg once daily, in reducing blood pressure and microalbuminuria in hypertensive patients with type 2 diabetes mellitus. Combination of both agents was well tolerated and more effective in reducing blood pressure than either drug alone (63). The ongoing CALM II study is investigating the effects of dual blockade, with candesartan cilexetil and lisinopril, on systolic blood pressure, left ventricular mass and function, and retinopathy in hypertensive patients with diabetes mellitus (1).

There was no significant difference between candesartan and lisinopril in their effects on renal potassium in hypertensive patients with type II diabetes mellitus and preserved renal function. Whether there are differences between the drug classes in renal impairment remains to be determined (83).

In a randomized, double-blind, controlled, parallel-group trial in 96 patients with mild hypertension and type 2 diabetes mellitus, who were not treated with hypercholesterolemic drugs, perindopril, 4 mg once daily, or candesartan cilexetil, 16 mg once daily, effectively lowered blood pressure. Perindopril, but not candesartan, improved some of the metabolic parameters in this special population of patients (20).

In obese hypertensive patients, candesartan cilexetil, 8 to 16 mg, once daily, but not hydrochlorothiazide, 25 or 50 mg/d, once daily, appeared to improve insulin sensitivity (35).

Pleiotropic effects of candesartan were demonstrated in a randomized, double-blind, placebo-controlled, crossover study in 45 hypertensive patients. Candesartan reversed

endothelial dysfunction: it improved vasodilator responses, fibrinolysis, reduced oxidant stress and the levels of inflammatory cytokines (45).

Few data exist on the effect of candesartan on clinically relevant endpoints. The Study on Cognition and Prognosis in the Elderly (SCOPE), a prospective, double-blind, randomized, parallel-group study, evaluated candesartan-based antihypertensive treatment vs. open labelled active antihypertensive therapy in almost 5,000 elderly hypertensive patients. Candesartan significantly reduced non-fatal stroke by 27.8% and blood pressure by 21.1/10.8 mm Hg vs. 18.5/9.2 mmHg. Major cardiovascular events were moderately but non-significantly reduced. Cognitive function was well maintained in the presence of substantial blood pressure reduction (49). According to a sub-analysis of the SCOPE study, cognitive function was positively associated with higher well-being and higher utility value, but was unrelated to the occurrence of subjective adverse symptoms (19).

In summary, candesartan cilexetil is an effective antihypertensive agent. Blood pressure reduction by candesartan is as least as effective as that by established agents of the same or other classes. Whether or not candesartan is superior in affecting relevant clinical endpoints such as mortality or morbidity from complications of hypertension, remains to be determined in future studies. As shown in the SCOPE study, add-on antihypertensive treatment with candesartan is likely to reduce non-fatal stroke and possibly major cardiovascular events in elderly hypertensive patients.

Heart failure

Angiotensin converting enzyme inhibitors (ACEIs) have been unequivocally shown to reduce all cause mortality in patients with chronic heart failure (CHF) and underlying

impaired left ventricular systolic function. The same holds true for the reduction of morbidity, as manifested by hospital admissions. ACEIs after myocardial infarction reduce the risk of all cause mortality and major clinical events (60). Therefore, angiotensin receptor blockers (ARBs) may at least theoretically be equally or even better suited for these indications as they appear to have similar efficacy, but are better tolerated than ACEIs.

This question was first addressed in a trial with an ARB, losartan. The ELITE study (*Evaluation of Losartan In The Elderly*) was a relatively small study set up to compare tolerability (assessed by changes of renal function) of losartan with that of captopril in patients over 65 years of age and NYHA class II – IV heart failure. A lower mortality was found for the losartan group, however, the trial was not designed to test this hypothesis (80). ELITE II was a repeat of ELITE but much larger with longer term follow-up and properly powered to examine mortality (primary endpoint). The study was designed as a superiority trial and did not show that losartan is better than captopril. The trial was not powered to demonstrate equivalence (81).

ARBs, like ACEIs, have favorable acute and chronic neurohumoral and hemodynamic actions in chronic heart failure patients (60): e.g. the RESOLVD (*Randomized Evaluation of Strategies for Left Ventricular Dysfunction*) pilot study has shown a better prevention of left ventricular remodeling by a combination of candesartan and enalapril than for either drug alone (58). The STRETCH (*Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure*) study showed that candesartan can dose-dependently improve exercise tolerance in CHF (84). Mitrovic et al. (62) assessed the short-term and long-term effects of candesartan on hemodynamics, neurohormones, as well as clinical symptoms, in patients with CHF in a multicenter, double-blind parallel-group study in 218 patients (NYHA II or III; ejection fraction <40%; pulmonary capillary wedge pressure >13 mmHg) who were treated for 12 weeks with placebo or candesartan 2, 4, 8 or 16 mg/day.

Hemodynamic measurements were performed by right heart catheterization after a single (day 1) and repeated (3-months) treatment. There was no excess of deaths in any treatment group. Candesartan was safe and well-tolerated at all doses. Single and multiple doses had a sustained, significant and dose-dependent reduction in pulmonary capillary wedge pressure (PCWP) and mean pulmonary arterial pressure. Candesartan led to the expected compensatory increase of angiotensin II levels and plasma renin activity and a corresponding decrease of aldosterone plasma concentration, demonstrating a sustained and effective blockade of the renin-angiotensin system over the entire treatment period.

The clinical outcome of RESOLVD did not, however, support superiority of candesartan or the combination of candesartan and enalapril over enalapril alone. Moreover, the study was stopped prematurely by its safety committee due to a higher mortality in the candesartan groups. The RESOLVD patient group participated later in a trial comparing candesartan or enalapril, the combination of both, candesartan plus metoprolol, enalapril plus metoprolol, and candesartan plus enalapril plus metoprolol (59). The triple combination had a minor effect on cardiac function only.

A further recent small sample size trial (ARCH-J: Assessment of Response to Candesartan in Heart failure in Japan) showed in patients with CHF (double-blind, placebo-controlled, randomized), who received no ACEI therapy, that candesartan cilexetil, at 8 mg/d over 6 months, reduced progression of CHF and significantly improved hemodynamics (54). The study was prematurely terminated after the second interim safety analysis when the differences between placebo and candesartan became significant. It remains unclear why the involved IRB consented to a protocol that offered CHF patients placebo instead of an ACEI as the proven state-of-the-art treatment and an appropriate comparator.

The CHARM (*Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity*) study program comprised three trials (93): (1) CHARM “Alternative” in ACE-I intolerant patients (34), (2) CHARM “Added” in ACE-I treated patients (61), and (3) CHARM “Preserved” in patients with preserved left ventricular systolic function (104). The SPICE trial (*Study of Patients Intolerant of Converting Enzyme inhibitors*) was a pilot study for CHARM “Alternative” that compared placebo to candesartan in patients intolerant of an ACEI. There was no significant difference in the proportion of placebo and candesartan treated patients remaining on treatment for three months (33). Candesartan was well tolerated by patients viewed to be ACEI intolerant by their physicians.

The CHARM program included a total of 7601 patients (76). The patients` characteristics are given in Table 2 and the results are summarized in Table 3. All patients suffered from CHF NYHA class II-IV. The studies were carried out in 618 study centers, an average of 6 patients per center, a fact which may enhance the selection bias. The target dose was 32 mg candesartan cilexetil, daily. Based on our knowledge of the dose-response curve for candesartan in hypertensive patients the dose appears to be unusually high. The follow-up was nearly 100%. The primary endpoint in each of the three trials was cardiovascular death or unscheduled hospitalization due to heart failure and all cause mortality in the overall program. Secondary endpoints were non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation and diabetes mellitus.

CHARM “Overall” did not show a significant difference in the primary endpoint (mortality) between ARB and placebo treatment (76) and demonstrated only a tendency toward a better effect with candesartan ($p = 0.055$).

The CHARM “Alternative” included patients who did not tolerate ACEIs prior to the trial, mostly due to cough, hypotension, renal impairment, and angioedema/anaphylaxis (34).

In 59% of these patients the target dose of candesartan was reached. Thirty percent of patients withdrew from candesartan during the study (29% from placebo). One-half of these 30% had objective adverse drug reactions: hypotension (3.7%), critical increase of creatinine (6.1%), hyperkalemia (1.9%), cough (0.2%), angioedema (0.1%). The combined endpoint was reduced to an extent as was expected for treatment with an ACEI (91).

In CHARM “Added” trial 96% of the included patients had been already on the optimal dose of an ACEI. Sixty-one percent reached the target dose of candesartan (61). The addition of candesartan slightly improved prognosis (Table 3), even in those patients who were on beta blockers. This is in contrast to the findings of the Val-HeFT trial (16). There were fewer myocardial infarctions in the candesartan-treated group (3.4% vs 7.5%; $p = 0.012$). Twenty-five percent of the patients on candesartan withdrew from the study (18% on placebo). Seven percent of patients on candesartan had a critical increase of creatinine (doubling of the prestudy value; 6% on placebo), additional medication with spironolactone raised creatinine levels critically in 11%.

CHARM “Preserved” trial investigated patients with left ventricular ejection fraction of $\geq 40\%$ (104). Only one-fifth of these patients received an ACEI in the beginning and at the end of the study. The effect of candesartan, administered with an ACEI was not significantly different from that of candesartan with placebo (Tables 3). Adjustment to preexisting risk factors made the reduction of hospital admissions due to addition of candesartan statistically significant. Adverse drug reactions were reported more often in the candesartan group (17.8% vs 13.5%).

This impressive trial program shows that ARB can be a meaningful replacement therapy in cases of ACEI intolerance. Whether this is a class effect or not is impossible to decide given the current database. Comedication with an ARB may be effective, however, the

treatment with beta blockers, a proven standard therapy in CHF, was not sufficient in the CHARM “Added” trial. As long as the left ventricular function is preserved, ARBs do not appear to have a major therapeutic impact. This finding is somewhat unexpected. Up to now candesartan has not been approved for the treatment of CHF. Thus, for the time being, ACEIs remain the standard treatment of CHF, unless not tolerated. In these cases ARBs have been shown to provide therapeutic benefit.

Stroke

The ACCESS study (*Acute Candesartan Cilexetil Evaluation in Stroke Survivors*), a multi-center randomized double-blind placebo-controlled trial, was designed to evaluate the safety of modest antihypertensive treatment in patients with acute cerebral ischemia. Patients with motor paresis and initial systolic blood pressure >200 mmHg and/or diastolic blood pressure >110 mmHg or mean blood pressure of two measurements >180 mmHg and/or >105 mmHg, respectively, were included. The combined secondary endpoint was mortality, cerebral and/or cardiovascular complications. The trial was stopped prematurely after the recruitment of 349 patients (500 planned) due to an imbalance in end-points: Cumulative 12-months mortality and the number of vascular events differed significantly in favor of the candesartan group (odds ratio 0.475; 95% CI 0.252 to 0.895). There were no cardiovascular or cerebrovascular events as a result of hypotension (87).

Miscellaneous indications

Migraine

The ACE inhibitor lisinopril has been found to reduce the incidence of frequent migraine attacks (86). It has been suspected that this effect may be due to its ability to reduce the levels of angiotensin II. A meta-analysis involving 12,000 patients indicated that the risk of headache was about one-third lower in users of ARBs compared with those taking placebo (27). There is a single prospective placebo-controlled, monocenter study using 16 mg/day candesartan cilexetil for two 12-week periods. Candesartan was associated with a significant reduction in the number of days with migraine (from 12.6 to 9 per 12 weeks), as well as reduced severity, disability, and number of days on sick leave (100). The rate of responders to candesartan (>50% reduction in days with migraine) was 40.4%. The exact mechanism of action of candesartan in migraine is unknown. Candesartan is not approved in any country for the treatment of migraine.

Bronchial asthma

There are animal data showing that AT₁ receptors are involved in antigen-induced airway hyperresponsiveness, eosinophil accumulation and angiotensin-induced bronchoconstriction. AT₁ receptors are expressed in human lung tissue. Myou et al. (66) carried out a pilot study with methacholine provocation test in patients with stable asthma. PC₂₀-FEV₁ values increased significantly after a one-week treatment with 8 mg candesartan daily. The decrease of blood pressure was not correlated with the change of PC₂₀-FEV₁. This trial suggests that AT₁ receptors are involved in bronchial hyperresponsiveness.

Adverse drug reactions and tolerability

Candesartan (up to 32 mg/day) was, similarly to other ARBs, well tolerated in clinical trials for all indications studied. Some of the studies involved, however, only small numbers of patients (40, 21, 78, 47, 52, 2, 102).

In patients with mild to moderate hypertension during five randomized, double-blind, placebo-controlled clinical trials conducted before approval of the drug, adverse events during candesartan cilexetil plus hydrochlorothiazide therapy (up to 16/25 mg, once daily) were uncommon. Serious adverse events were observed in 1.6% of patients on combination and in 2.1% on placebo. The most commonly reported adverse events (cumulative 8-week incidence) were headache (3.2 vs 5.5%, drug vs placebo), backpain (3.0 vs 2.4%), dizziness (2.6 vs 1.2%) and upper respiratory tract infection (2.5 vs 1.4%) (9). Cough was infrequent in comparison with placebo (1.6% with candesartan vs. 1.1% with placebo) (8). In a placebo-controlled trial of 154 patients with a confirmed history of ACEI-induced cough, treatment with candesartan cilexetil, 8 mg/day over 8 weeks, significantly lowered the frequency and severity of dry cough to a level not significantly different from that reported in placebo recipients (97). This finding has been confirmed in a comparative trial of enalapril and calcium antagonists. Pulmonary function and bronchial hyperresponsiveness were unaffected (96).

Results from a randomized, double-blind, multicenter study comparing candesartan cilexetil and lisinopril in combination with low dose hydrochlorothiazide showed that the incidence of cough (23.1 vs 4.6%) was higher with the lisinopril combination (57). The tolerability profile during the long-term studies was similar to that of short-term clinical trials and did not appear to be related to either gender or age (88).

A pooled safety analysis on five randomized, placebo-controlled studies in patients with CHF (1893 subjects of whom 1287 received candesartan and 606 placebo) showed that all cause mortality and unexpected deaths and hospitalizations for acute deterioration of CHF, chronic progression of CHF and other intercurrent events or accidental injury/attempted suicide were not different or in some measures (hospitalizations) statistically significant in favor of candesartan (26). The ARCH-J study confirmed an effect of the ARB on clinical outcome of chronic heart failure, the candesartan group had more adverse events (31.1 %) than the placebo group (21.1%). Adverse events were mainly due to its pharmacodynamic properties including hypotension and postural lightheadedness (54).

Neither hyperuricemia nor hypokalemia have been associated with candesartan therapy (68). In comparison with calcium channel blockers peripheral edema is infrequent (8.9% with candesartan vs 22.1% with amlodipine) (44). Candesartan cilexetil, 2 to 16 mg/day, has been rarely associated with minor and transient increases in serum liver enzyme levels (8, 88).

The CHARM trials confirmed our current knowledge of adverse events with candesartan. The CHARM-Added trial (61) reported two cases of angioedema in patients receiving candesartan and an ACEI. In 7% of the candesartan-treated patients creatinine at least doubled from the baseline (6% in placebo-treated patients). Among patients taking spironolactone, creatinine at least doubled in 11% (candesartan) vs 4% (placebo). In the candesartan group 3% developed potassium concentrations of 6 mmol/L or higher compared with 1% in the placebo group (spironolactone group: 4% candesartan vs 1% placebo).

In CHARM-Alternative (34) angioedema occurred in 3 patients (candesartan only, none under placebo) who had a history of ACE intolerance because of angioedema or

anaphylaxis. Serum creatinine at least doubled in 5.5% (candesartan) vs 1.6% (placebo). Potassium levels increased to 6 mmol/L or higher in 3% (candesartan) vs 1.3% (placebo).

CHARM-Preserved (104) reported at least doubling of creatinine in 6% of candesartan-treated and in 3% of placebo-treated patients. Potassium levels of 6 mmol/L or higher were noted in 2% of candesartan- vs 1% of placebo-treated patients.

There is a report of a few cases of psoriasis in patients treated with ARBs, including candesartan, within 6 to 9 weeks after start of medication. In some of these patients a preexisting psoriasis was activated and in others this disease appeared for the first time (53).

Basile et al. (6) reported a case of severe hepatotoxicity associated with ductopenia in a patient treated with candesartan.

Rare cases of Henoch-Schönlein purpura have been reported in patients treated with losartan (13). Recently, a similar syndrome with rash and acute nephritis has been reported for the first time in a patient treated with candesartan (65).

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ADDENDUM:

Sources: Medical literature published in English or German language since 1990 on candesartan was identified using Medline and Cochrane Library, supplemented by Biosis. Additional references were identified from the reference lists of published articles and hand searches.

Search strategy: Medline search terms were Candesartan, Candesartan cilexetil, Candesartan hexetil, CV 11974, H 212/91 and TCV 116. Biosis search term was Candesartan. Searches were last updated February 27th , 2004.

Selection: Studies in patients with any diseases who received candesartan alone or in combination. Inclusion of studies was based mainly on the methods of trials. When available, large, controlled trials with appropriate statistical methodology were preferred. Relevant pharmacological, pharmacodynamic and pharmacokinetic data were included.

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Legend to figure

Fig. 1: Chemical structure of the prodrug candesartan cilexetil, (TCV-116; (\pm) -1-(cyclohexyloxycarbonyloxy)-ethyl-2-ethoxy-1-((2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylate) and its active metabolite candesartan (CV11974; 2-ethoxy-1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-1H-benzimidazole-7-carboxylic acid).

TABLE 1: Pharmacokinetic properties of AT₁ receptor antagonists in healthy volunteers.

Drugs	Bioavailability %	Protein binding %	Active metabolite	Half-life h	Excretion %	Daily dosage mg, (starting/ maximal)	Effect of food
Losartan	33	98	EXP3174	2 (6-9)	EXP3174 Renal 50 Biliary 50	50/100	C _{max} ↓, AUC↓
Valsartan	25	95	No	9	renal 30 biliary 70	80/160	C _{max} ↓, AUC↓
Irbesartan	70	95	No	11-15	renal 20 biliary 80	150/300	none
Candesartan-cilexetil	42	99.5	Candesartan	3.5-11	Candesartan renal 60 biliary 40	4/16 (32)	none
Telmisartan	43	> 99	No	24	biliary 98	40/80	C _{max} ↓
Olmesartan-medoxomil	25	> 99	Olmesartan	10-15	Olmesartan renal 40 biliary 60	10/40	none
Eprosartan	15	98	No	5-7	renal 10 biliary 90	600	C _{max} ↓, AUC↓

Adapted from references 32 and 94

TABLE 2: Patient characteristics in CHARM trials

	CHARM Added*	CHARM Alternative*	CHARM Preserved*	CHARM Overall*
<i>Mean age, y</i>	64	67	67	66
<i>Women %</i>	21	32	40	32
<u>NYHA classes %</u>				
II	24	48	60	45
III	73	49	38	52
IV	3	3	2	3
<i>Mean left ventricular ejection fraction</i>	28	30	54	39
<u>Underlying disease, %</u>				
Myocardial infarction	56	61	44	53
Diabetes mellitus	30	27	28	28
Hypertension	48	50	64	55
Atrial fibrillation	26	25	29	27
<i>Blood pressure mmHg</i>	125/75	130/77	136/78	131/77
<i>Heart rate , L/min</i>	74	74	71	73
<u>Basal therapy, %</u>				
ACEI	100	0	19	41
Beta-Blocker	56	55	56	55
Diuretic	90	86	75	83
Spironolactone	17	24	12	17
Digitalis	58	46	28	43
Aspirin	52	58	58	56
Statin	41	41	42	42

Adapted from Ref. 76

* CHARM added: ACE-I + Candesartan

CHARM Alternative: Candesartan instead of ACEI

CHARM preserved: Candesartan in patients with left ventricular function of > 40%

CHARM overall: Results from all CHARM studies taken together

TABLE 3. Results of CHARM trials

Parameter	CHARM Added	CHARM Alternative	CHARM Preserved	CHARM Overall
No. of patients	2548	2028	3023	7601
Length of follow-up, months	41	33.7	36.6	37.7
Cardiovascular deaths %	23.7 vs 27.3*	21.6 vs 24.8 (ns)	11.2 vs 11.3 (ns)	18.2 vs 20.3*
Hospitalization due to CHF, %	24.2 vs 28*	20.4 vs 28.2*	15.9* vs 18.3 (ns)	19.9 vs 24.2*
Combined end point, %	37.9 vs 42.3*	33 vs 40*	22 vs 24.3 (ns)	30.2 vs 34.5*
NNT/yr for prevention of combined end point	85	40	132	73

Modified from ref. 3

*stat. significant, ns = not significant, NNT = number needed to treat

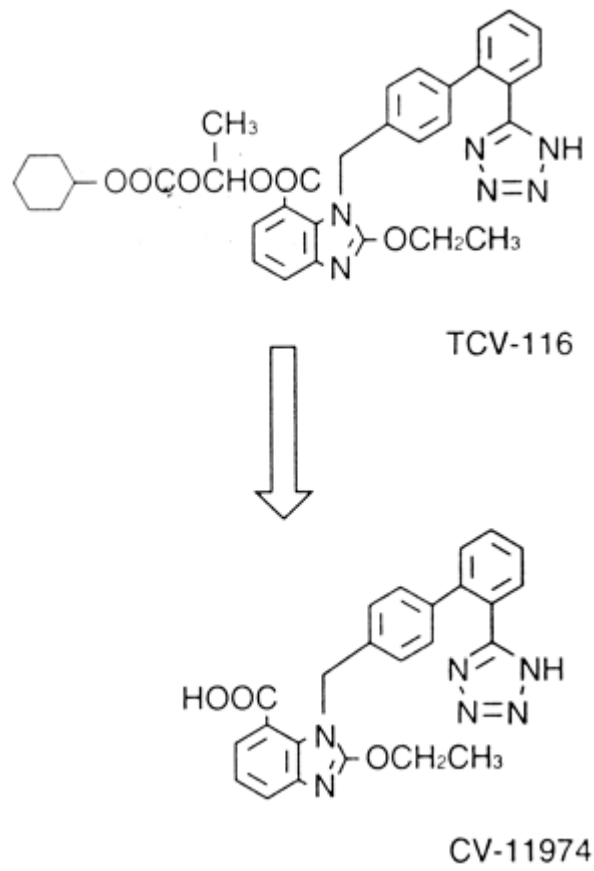


Fig. 1