REVIEW

Differential clinical profile of candesartan compared to other angiotensin receptor blockers

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Abstract: The advantages of blood pressure (BP) control on the risks of heart failure and stroke are well established. The renin-angiotensin system plays an important role in volume homeostasis and BP regulation and is a target for several groups of antihypertensive drugs. Angiotensin II receptor blockers represent a major class of antihypertensive compounds. Candesartan cilexetil is an angiotensin II type 1 (AT[1]) receptor antagonist (angiotensin receptor blocker [ARB]) that inhibits the actions of angiotensin II on the renin-angiotensin-aldosterone system. Oral candesartan 8–32 mg once daily is recommended for the treatment of adult patients with hypertension. Clinical trials have demonstrated that candesartan cilexetil is an effective agent in reducing the risk of cardiovascular mortality, stroke, heart failure, arterial stiffness, renal failure, retinopathy, and migraine in different populations of adult patients including patients with coexisting type 2 diabetes, metabolic syndrome, or kidney impairment. Clinical evidence confirmed that candesartan cilexetil provides better antihypertensive efficacy than losartan and is at least as effective as telmisartan and valsartan. Candesartan cilexetil, one of the current market leaders in BP treatment, is a highly selective compound with high potency, a long duration of action, and a tolerability profile similar to placebo. The most important and recent data from clinical trials regarding candesartan cilexetil will be reviewed in this article.

Keywords: angiotensin receptor blockers, candesartan, candesartan cilexetil, clinical trials, efficacy studies, safety, blood pressure

Introduction to the development and use of sartans in the treatment of cardiovascular disease

Hypertension is a major risk factor for morbidity and mortality through its effects on target organs like heart, brain, and kidneys. More intensive treatment for the effective control of blood pressure (BP) significantly reduces morbidity and mortality.[1,2] The renin angiotensin system (RAS) is a coordinated hormonal cascade of major clinical importance in the regulation of BP.[2] The principal peptide of RAS is angiotensin II, which acts by binding to one of the two major angiotensin II receptors AT(1) and AT(2). Angiotensin II through AT(1) receptor mediates a vast majority of biologically detrimental actions. Candesartan cilexetil is one of a number of drugs of the angiotensin II receptor blocker (ARB) class. Candesartan cilexetil is converted to the angiotensin II receptor antagonist candesartan during absorption from the gastrointestinal tract. The selective and competitive binding of candesartan to the AT(1) receptor prevents binding of angiotensin II, a key mediator in the renin-angiotensin system.[3,4] It was administrated for the first time in animal models in 1992 and in clinical trials 2 years later.[5,6] Its use has increased dramatically in the treatment of stroke,

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heart failure, diabetic renal disease, and most recently in preventing the development of or delaying the progression of diabetic retinopathy.[1–4]

Overview of differential pharmacology of candesartan compared to other sartans

ARBs do not modulate the amount of circulating angiotensin II; rather, they inhibit the binding of angiotensin II to AT(1). AT(1) receptors are located primarily in the vascular smooth muscle and adrenal glands. ARBs inhibit most of the biological effects of angiotensin II: contraction of vascular smooth muscle, pressor responses, thirst, aldosterone secretion, vasopressin release, release of adrenal catecholamines, augmentation of noradrenergic neurotransmission, increase of sympathetic tone, change in renal function, and cellular hypertrophy and hyperplasia. Because they do not have a direct effect on the angiotensin-converting enzyme (ACE), ARBs do not directly affect bradykinin; however, they may increase nitric oxide release and inhibit its degradation.[7,8]

ARBs differ in their AT(1) binding characteristics. Binding is classified as surmountable or insurmountable, according to the shifting of the angiotensin II concentration-response curves to the right. Surmountable antagonism does not change the maximal angiotensin II response; insurmountable antagonism reduces the response. Therefore, insurmountable binding cannot be overcome by increasing concentrations of angiotensin II.[9] The insurmountable behavior of candesartan is linked to the presence of a carboxyl group at its imidazole-derived moiety. But telmisartan and valsartan show insurmountable behavior despite the absence of a carboxyl group.[10]

The AT(1) receptor can be activated by mechanical stress through an angiotensin II-independent mechanism. Without the involvement of angiotensin II, mechanical stress not only activates extracellular signal-regulated kinases and increases phosphoinositide production in vitro, but also induces cardiac hypertrophy in vivo. Mechanical stretch induces association of the AT(1) receptor with Janus kinase 2, and translocation of G proteins into the cytosol. All of these events are inhibited by the AT(1) receptor blocker candesartan cilexetil. Candesartan cilexetil, olmesartan, and valsartan can stabilize the AT(1) receptor in an inactive state, called "inverse agonism", in the absence of angiotensin II, thereby attenuating cardiac hypertrophy, independent of BP reduction.[10–13] There is also another mechanism that explains the link between cardiac stretching and the AT(1) receptor.

Mechanical stress stimulates the secretion of angiotensin II from secretory granules through natural messengers inside cardiac myocites.[10]

There are some ARBs that can function as a partial agonist of peroxisome proliferator activator receptor gamma and improve carbohydrate and lipid metabolism, such as candesartan cilexetil and telmisartan, but only telmisartan can achieve this effect with therapeutic doses.[14]

The AT(2) receptor remains mysterious, especially in AT(2)-coupled interference with proinflammatory pathways. It is thought that effects mediated by the AT(2) receptor include inhibition of cell growth, fetal tissue development, modulation of extracellular matrix, neuronal regeneration, apoptosis, cellular differentiation, and, possibly, vasodilation and left ventricular hypertrophy. ARBs in clinical use are more than 10,000-fold selective for the AT(1) receptor versus the AT(2) receptor, with one of the highest selective being candesartan cilexetil.[10–13] The pharmacological properties of candesartan cilexetil and other ARBs are presented in Table 1.[10–15]

Clinical use and efficacy studies of candesartan cilexetil in comparison to other sartans

Several clinical trials have shown the efficacy of candesartan cilexetil in the treatment of patients with hypertension, left ventricular dysfunction, acute coronary syndrome, heart failure, arterial compliance, retinopathy, nephropathy, stroke, atrial fibrillation, and migraine, and also the cost effectiveness of candesartan cilexetil. Some of them are summarized in Table 2 and detailed after that.

Heart failure
CHARM-Added

The Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial investigated the efficacy of 32 mg candesartan cilexetil versus placebo in 2548 patients already being treated with an ACE inhibitor for chronic heart failure and a left ventricular ejection fraction less than 40%.[16] Patients were observed for a median of 41 months. The addition of candesartan cilexetil significantly reduced the primary outcome of cardiovascular death or hospitalization for chronic heart failure compared with placebo (38% vs 42%, HR: 0.85, $P = 0.011$). Candesartan cilexetil also reduced the need for multiple admissions for chronic heart failure, suggesting a sustained and durable benefit.

Table 1 Pharmacology and pharmacokinetics of angiotensin receptor blockers

	Candesartan	Losartan	Valsartan	Olmesartan	Telmisartan	Eprosartan	Irbesartan
Food Interaction	No	10% decrease in biov.	Not Significant	No	6%–20% decrease in biov.	Not significant	No
Drug–drug interaction that may require therapy modification	Amifostine Lithium Rituximab	Amifostine Lithium Fluconazole Nicardipine Sulfadiazine Rituximab	Amifostine Lithium Rituximab	Amifostine Lithium Rituximab	Amifostine Lithium Rituximab Digoxin	Amifostine Lithium Rituximab	Amifostine Lithium Rituximab
Dose in hepatic impairment	Lower dose in moderate hepatic failure	Lower dose	No change in dose	No change in dose	No change in dose	No change in dose	No change in dose
Dose in renal impairment	No change in dose	No change in dose	No change in dose	No change in dose	No change in dose	No change in dose	No change in dose
PPAR-G	Yes	Yes	None	None	Yes	None	Yes
AT(1) receptor binding	Insur	Sur	Insur	Insur	Insur	Sur	Insur
Dissociation $t_{1/2}$ (min)	120	Fast EXP = 30	17	75	25		7
Binding potency candesartan = 1	1	0.014 EXP = 0.45	0.17	0.73	0.083		0.15
AT(1) receptor selectivity versus AT(2)	A	C	C	A	C	B	B
Inverse agonism	Yes	None	Yes	Yes	None	None	None
Total daily dose (mg)	8–32	50–100	80–320	20–40	40–80	400–800	150–300
Number of doses (daily)	1–2	1–2	1–2	1	1	1–2	1
P450 metabolism	Not significant	CYP 2C9 and 3A4	Unknown	No	No	No	CYP 2C9
Protein binding	99%	High	95%	99%	99.5%	98%	90%
Half life (hours)	5–9	6–9	6	13	24	5–9	11–15
Time to peak serum (hours)	3–4	3–4	2–4	1–2	0.5–1	1–2	1.5–2
Excretion	Urine (26%)	Urine (10%)	Feces (83%)	Feces (50%) Urine (50%)	Feces (97%)	Feces (90%) Urine (7%)	Feces (50%) Urine (50%)
Time to BP effect (weeks)	2–4	3–6	4	1–2	4	2–3	2

Abbreviations: AT(1), angiotensin type 1 receptor; AT(2), angiotensin type 2 receptor; CYP, cytochrome; EXP, EXP3174, the active metabolite of losartan; PPAR-G, peroxisome proliferator activated receptor gamma; A, highest level of affinity; B, second in line after A; C, third in line after A and B; sur, surmountable; insur, insurmountable; Biov., bioavailability; BP, blood pressure.

CHARM–Alternative

This trial investigated whether 32 mg candesartan cilexetil would improve the clinical outcomes of 2028 patients with congestive heart failure and left ventricular systolic dysfunction (ejection fraction less than 40%) who were intolerant to ACE inhibitors.[17] Candesartan cilexetil significantly reduced the relative risk of cardiovascular mortality or hospital admission for heart failure by 23% compared with placebo (HR: 0.77, 95% CI: 0.67–0.89, $P = 0.0004$). The clinical benefit was also observed in patients with nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization. Importantly, hospitalization for worsening heart failure was reduced by 32% ($P < 0.0001$) with candesartan cilexetil.

CHARM-Preserved

This trial investigated whether 32 mg candesartan cilexetil could improve the clinical outcomes of 3023 patients with congestive heart failure and preserved left ventricular systolic dysfunction (ejection fraction higher than 40%).[18] Cardiovascular death did not differ between groups (170 vs 170), but fewer patients in the candesartan cilexetil group

Table 2 Clinical trials of candesartan cilexetil

Target	Study	Patient population and duration	Treatment added to standard therapy	Primary endpoint	Benefit
Heart Failure	CHARM–Added[16]	CHF, EF < 40% (41 months)	Candesartan + ACEI vs ACEI	Reduction in mortality and morbidity	Confirmed
	CHARM–Alternative[17]	CHF, EF < 40%, intolerant to ACEI (33.7 months)	Candesartan vs placebo	Reduction in mortality and hospital admission	Confirmed
	CHARM-Preserved[18]	CHF, EF > 40% (36.6 months)	Candesartan vs placebo	Reduction in mortality and hospital admission	Moderate confirmed
High blood pressure	TROPHY[19]	Prehypertension (4 years)	Candesartan vs placebo	Prevention HTN	Confirmed
	Five trials[20]	HTN ± DM (12–14 wks)	Candesartan vs placebo	Treatment HTN	Confirmed
	Candesartan comparative trial[21]	HTN + DM (3 months)	Candesartan vs telmisartan and valsartan	Treatment HTN	As good as the other two
	Candesartan comparative trial[22]	HTN and CHF Meta-analysis	Candesartan vs losartan	Treatment HTN	Better. Not cost-effective
Arterial elasticity	CALM II[23]	HTN + DM (12 months)	Candesartan + 20 mg lisinopril vs 40 mg lisinopril	Reduction in pulse pressure	Confirmed
	Large and small artery elasticity[24]	HTN + DM (6 months)	32 mg candesartan vs 16 mg candesartan vs placebo	Reduction in arterial elasticity	Confirmed
Renal protection	SECRET[25]	Renal graft + HTN (3 years)	Candesartan vs placebo	Reduction in mortality and graft failure	Confirmed
	CKD stage 4–5[26]	CKD stage 4–5 and BP < 140/90 mmHg (3 years)	Candesartan vs placebo	Reduction in mortality and hemodialysis prevention	Confirmed
	CKD stage 1–3[27]	CKD stage 1–3, DM, ALB (8 months)	Candesartan vs placebo	Reduction in ALB	Confirmed
Stroke	SCOPE[28]	Aged 70–89 years, HTN (3.7 years)	Candesartan vs placebo	Reduction in stroke and cognitive decline	Confirmed for stroke only
	ACCESS[29]	Early stroke, HTN (1 year)	Candesartan vs placebo	Reduction in mortality and morbidity	Confirmed
	SCAST[30]	Within first 30 hours after stroke (6 months)	Candesartan vs placebo	Better functional outcome	Worse than placebo
Retinal protection	DIRECT-Prevent 1[31]	No RTP + DM type 1, no HTN, no ALB (4 years)	Candesartan vs placebo	Prevention of RTP	Partially confirmed
	DIRECT-Protect 1[31]	RTP + DM type 1, no HTN, no ALB (4 years)	Candesartan vs placebo	Reduction in RTP	Partially confirmed
	DIRECT-Protect 2[32]	RTP+DM type 2, no HTN, no ALB (4 years)	Candesartan vs placebo	Reduction in RTP	Partially confirmed
New-onset diabetes prevention	CASE-J [33,34]	HTN + obesity	Candesartan vs amlodipine	Reduction in new-onset DM and mortality	Confirmed
Migraine	Prophylaxis[35]	Migraine (12 wks)	Candesartan vs placebo	Reduction in no. of days with headache	Confirmed
Atrial fibrillation	J-RHYTHM II[36]	Paroxysmal AF + HTN (1 year)	Candesartan vs Amlodipine	Reduction in frequency of AF episodes	Confirmed but not better

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ALB, albuminuria; ARB, angiotensin receptor blocker; BP, blood pressure; CHF, chronic heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; EF, ejection fraction; HTN, hypertension; RTP, retinopathy. Clinical studies: ACCESS, Acute Candesartan Cilexetil Therapy in Stroke Survivors; CALM II, Candesartan and Lisinopril Microalbuminuria Trial II; CASE-J, Candesartan Antihypertensive Survival Evaluation in Japan; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality; DIRECT, DIabetic REtinopathy Candesartan Trials; J-RHYTHM II, Japanese Rhythm Management Trial II for Atrial Fibrillation; SCAST, Candesartan for Treatment of Acute Stroke; SCOPE, Study on Cognition and Prognosis in the Elderly; SECRET, Study on Evaluation of Candesartan Cilexetil after Renal Transplantation; TROPHY, Trial of Preventing Hypertension.

than in the placebo group were admitted to hospital for congestive heart failure once (230 vs 279, $P = 0.017$) or multiple times. The clinical benefit was also observed in patients with nonfatal myocardial infarction, and nonfatal stroke.

Hypertension
TROPHY

The trial of preventing hypertension (TROPHY) investigated whether candesartan cilexetil along with lifestyle modifications prevents worsening of prehypertension.[19] A total of 809 participants with repeated measurements of systolic BP (SBP) of 130–139 mmHg and diastolic BP (DBP) of 89 mmHg or lower, or SBP of 139 mmHg or lower and DBP of 85–89 mmHg, were randomly assigned to receive 2 years of candesartan cilexetil (n = 409) or placebo (n = 400), followed by 2 years of placebo. All data on 772 participants (391 in the candesartan cilexetil group, and 381 in the placebo group; mean age, 48.5 years; 59.6% men) were available for analysis. During the first 2 years, hypertension developed in nearly two-thirds of participants (n = 154) in the placebo group and 53 of those in the candesartan cilexetil group (relative risk reduction 66.3%, $P < 0.001$). After 4 years, hypertension had developed in 240 participants in the placebo group and 208 of those in the candesartan cilexetil group (relative risk reduction 15.6%, $P < 0.007$).

Candesartan cilexetil in the management of BP in diabetic and nondiabetic hypertensive patients

A selection of five randomized double-blind clinical trials in which patients were treated for hypertension with candesartan cilexetil were analyzed.[20] All of these were similar in design: (1) a 4-week placebo run-in period, (2) a 4- to 6-week period (V1) with candesartan cilexetil 8 mg once daily, after which the dosage was doubled if BP was not normalized (BP > 140/90 or BP > 130/80 mmHg in diabetes), and (3) a 4- to 6-week period (V2) with candesartan cilexetil 8 or 16 mg once daily. Efficacy was measured at V1 and V2. Seven hundred and two patients were screened. The population consisted of 397 males (56.6%) with a mean age of 60 ± 11 years, with 153 diabetic (21.8%) and 549 nondiabetic (78.2%) patients. At baseline, mean BP values were 160/94/65 mmHg for SPB, DBP, and pulse pressure (PP) respectively, with differences between diabetic and nondiabetic patients. SBP, DBP, and PP values showed a significant reduction at V1 ($P < 0.001$) and V2 ($P < 0.001$) compared with baseline for all hypertensive patients. Mean changes at V2 in SBP and PP values were higher in diabetic

than nondiabetic patients ($P < 0.001$), and to a lesser degree on DBP values ($P = 0.034$).

Candesartan cilexetil versus telmisartan or valsartan

A total of 308 hypertensive patients with diabetes were enrolled in our multicenter, randomized, open-label study.[21] The patients received 40 mg telmisartan, 8 mg candesartan cilexetil, or 80 mg valsartan for 3 months, and the data for 227 patients (telmisartan: n = 74, candesartan cilexetil: n = 79, and valsartan: n = 74) were analyzed. The SBP and DBP significantly decreased in all the groups at the end of the study; the decrease was comparable among the three groups.

Candesartan cilexetil versus losartan

This meta-analysis compared and analyzed as the primary end point candesartan cilexetil and losartan in the management of hypertension and heart failure.[22] The secondary objective was to model their comparative incremental cost-effectiveness in a UK National Health Service setting. Fourteen studies (eight of hypertension and six of heart failure) were included. Eight and zero trials compared candesartan cilexetil directly with losartan in the treatment of hypertension and heart failure, respectively. A between-treatment difference of −1.96 mmHg (95% CI: −2.40 to −1.51) for trough DBP and −3.00 mmHg (95% CI: −3.79 to −2.22) for trough SBP in favor of candesartan cilexetil was observed. Based on this differential, a 10-year Markov model estimates the cost per quality-adjusted life-year gained to exceed £40,000 for using candesartan cilexetil in place of generic losartan. Candesartan cilexetil reduces BP to a slightly greater extent when compared with losartan, however, such a difference is unlikely to be cost-effective based on current acquisition costs. Robust evidence supporting the superiority of candesartan cilexetil over losartan in the treatment of heart failure was not found.

Arterial compliance
CALM II

Candesartan And Lisinopril Microalbuminuria trial II (CALM) II was a 12-month prospective, randomized, parallel-group, double-masked study that included 75 type 1 and type 2 diabetic subjects with hypertension.[23] Participants were randomized to treatment with either high-dose lisinopril (40 mg once daily [od]) or for dual blockade treatment with candesartan cilexetil (16 mg od) and lisinopril (20 mg od). The effect of 12 months of dual blockade with candesartan cilexetil and lisinopril versus high-dose lisinopril monotherapy on ambulatory PP of 51 participants with type 2 diabetes who

completed the full 12-month study period with successful ambulatory BP measurements at both baseline and follow-up visits was examined. Compared with lisinopril monotherapy, dual blockade treatment caused a highly significant reduction in 24-hour PP levels (-5 ± 5 mmHg, $P = 0.003$), albeit the difference in the BP lowering effect between the treatment groups did not differ significantly for 24-hour SBP ($P = 0.21$) or DBP ($P = 0.49$). Dual blockade treatment significantly lowered 24-hour SBP (-5 ± 11 mmHg, $P = 0.03$), but not 24-hour DBP (-2 ± 7 mmHg, $P = 0.29$), whereas in the lisinopril group, the opposite effect was observed (24-hour SBP -1 ± 9 mmHg, $P = 0.45$; 24-hour DBP -3 ± 7 mmHg, $P = 0.03$).

Arterial elasticity

The effect of candesartan cilexetil on arterial elasticity, inflammatory, and metabolic parameters in hypertensive patients with multiple cardiovascular risk factors was assessed.[24] 69 hypertensive patients were randomized into three groups: group 1 included patients treated with high doses of candesartan cilexetil (32 mg), group 2 included patients treated with conventional doses of candesartan cilexetil (16 mg), and group 3 included patients who received antihypertensive treatment other than ARBs or angiotensin-converting enzyme inhibitors. Arterial elasticity was evaluated using pulse wave contour analysis method (HDI CR 2000, Eagan, Minnesota). In patients treated with high doses of candesartan cilexetil: large artery elasticity index (LAEI) increased from 8.6 ± 2.8 to 16.6 ± 5.1 mL/mmHg $\times$ 100 after 6 months of treatment ($P < 0.0001$). Small artery elasticity index (SAEI) increased from 2.7 ± 1.3 to 5.9 ± 2.8 mL/mmHg $\times$ 100 ($P < 0.0001$). Systemic vascular resistance decreased from 1881.5 ± 527.5 to 1520.9 ± 271.8 ($P < 0.0006$). In patients treated with conventional doses of candesartan cilexetil: LAEI index increased from 11.0 ± 3.5 to 14.4 ± 3.2 mL/mmHg $\times$ 100 ($P < 0.0001$). SAEI increased during the study from 3.7 ± 1.4 to 5.4 ± 2.1 mL/mmHg $\times$ 100 ($P < 0.0001$). Systemic vascular resistance decreased from 1699.8 ± 327.6 to 1400.7 ± 241 ($P < 0.0001$). In the control group: neither LAEI nor SAEI improved during the treatment period. Although similar reduction in BP was observed in all three groups, both LAEI and SAEI improved only in patients treated with ARBs.

Renal protection
SECRET

The Study on Evaluation of Candesartan cilexetil after Renal Transplantation (SECRET): an international multicenter, double-blind, randomized investigation of candesartan cilexetil versus placebo in renal allograft recipients was originally designed to study 700 patients for 3 years.[25] The candesartan cilexetil dose was escalated from 4 to 16 mg daily, followed by addition of comedication, if needed, with the aim of achieving a DBP < 85 mmHg. The primary efficacy variable was a composite of all-cause mortality, cardiovascular morbidity, and graft failure. SECRET was stopped prematurely as the primary event rate was much lower than expected. At that point, 502 patients were enrolled; 255 received candesartan cilexetil and 247 placebo. Thirteen primary events had occurred in each group. Control of both SBP and DBP was better in the candesartan cilexetil group. Urinary protein excretion and protein/creatinine ratio decreased on candesartan cilexetil but increased on placebo. Serum creatinine and potassium were increased in candesartan cilexetil patients, but these changes were generally small.

Patients with stage 4–5 chronic kidney disease

Candesartan cilexetil was administered to 13 patients (candesartan group, n = 7; control group, n = 6) with a serum creatinine level of 2.52–5.95 mg/dL whose BP had been maintained below 140/90 mmHg by the use of drugs other than ARBs.[26] Routine measurements were conducted for 48 weeks, and renal survival analysis was observed for up to 3 years with the endpoints being doubling of the serum creatinine level, entry to hemodialysis, or death. The results were compared with those of the control group that was not treated with ARBs. No significant changes were observed in BP in either group. Proteinuria significantly decreased from 0.95 ± 0.51 to 0.39 ± 0.12 g/day (paired t test, $P = 0.033$) in the ARB group, but did not change in the control group. Creatinine clearance in the control group decreased significantly from 16.2 ± 5.7 to 10.4 ± 4.8 mL/min per 1.73 m^2 (paired t-test, $P = 0.011$), but did not change in the other group. Thus, the slopes of the reciprocal serum creatinine values became less steep in the candesartan cilexetil group as compared with the control (-0.002 ± 0.015 vs -0.025 ± 0.015 dL/mg per month; unpaired t-test, $P = 0.019$). Kaplan–Meier analysis revealed that ARBs exhibited more favorable renal outcomes at 3 years (log-rank, $P = 0.025$). No serious adverse events were noted in the study. These results show that candesartan cilexetil reduces proteinuria and protects renal function even in advanced renal failure.

Patients with mild-to moderate renal failure, type 2 diabetes, and proteinuria

A total of 23 hypertensive patients with type 2 diabetes and nephropathy were enrolled in this double-blind,

randomized cross-over trial with four treatment periods, each lasting 2 months.[27] Each patient received placebo and candesartan cilexetil: 8, 16, and 32 mg daily in random order. Antihypertensive medication was discontinued before enrollment, except for long-acting furosemide, which all patients received throughout the study in median (range) doses of 40 (30–160) mg daily. Endpoints were albuminuria, 24-hour BP, and glomerular filtration rate (GFR). Values obtained during placebo treatment: albuminuria (geometric mean [95% CI]) 700 (486–1007) mg/24-hour; 24-hour BP (mean ± SE) 147 ± 4/78 ± 2 mmHg, and GFR 84 ± 6 mL/min/1.73 m². All three doses of candesartan cilexetil significantly reduced albuminuria and 24-hour BP compared with placebo. Mean reductions in albuminuria were 33% (95% CI: 21–43), 59% (95% CI: 52–65), and 52% (95% CI: 44–59) with increasing doses of candesartan cilexetil. Albuminuria was reduced significantly more by the two highest doses than by the lowest dose ($P < 0.01$); 24-hour SBP was reduced by 9 (95% CI: 2–16), 9 (95% CI: 2–16), and 13 (95% CI: 6–20) mmHg, and 24-hour DBP was reduced by 5 (95% CI: 2–8), 4 (95% CI: 1–7), and 6 (95% CI: 3–9) mmHg with increasing doses of candesartan cilexetil. There were no significant differences in the reductions in BP between the three doses. GFR was decreased by approximately 6 mL/min/1.73 m² by all three doses of candesartan cilexetil ($P < 0.05$ vs placebo).

Stroke
SCOPE
The Study on COgnition and Prognosis in the Elderly (SCOPE) assessed whether candesartan cilexetil-based antihypertensive treatment in elderly patients with mildly to moderately elevated BP confers a reduction in fatal and nonfatal stroke, cardiovascular events, cognitive decline, and dementia.[28] The study included 4964 patients aged 70–89 years with SBP 160–179 mmHg, and/or DBP 90–99 mmHg. A total of 527 centers in 15 countries participated in the study. Patients were assigned randomly to receive candesartan cilexetil or placebo, with open-label active antihypertensive therapy added as needed. As a consequence, active antihypertensive therapy was extensively used in the control group (84% of patients). Mean follow-up was 3.7 years. BP fell by 21.7/10.8 mmHg in the candesartan cilexetil group and by 18.5/9.2 mmHg in the control group. A first major cardiovascular event occurred in 242 candesartan cilexetil patients and in 268 control patients; risk reduction with candesartan cilexetil was 10.9% (95% CI: −6.0 to 25.1, $P = 0.19$). Candesartan cilexetil-based treatment reduced nonfatal stroke by 27.8% (95% CI: 1.3 to 47.2, $P = 0.04$),

and all stroke by 23.6% (95% CI: −0.7 to 42.1, $P = 0.056$). There were no significant differences in myocardial infarction and cardiovascular mortality. Mean MMSE score fell from 28.5 to 28.0 in the candesartan cilexetil group and from 28.5 to 27.9 in the control group ($P = 0.20$). The proportions of patients who had a significant cognitive decline or developed dementia were not different in the two treatment groups.

ACCESS
The Acute Candesartan Cilexetil therapy in Stroke Survivors (ACCESS) study was designed to assess the safety of modest BP reduction by candesartan cilexetil in the early treatment of stroke.[29] 500 patients were recruited in a prospective, double-blind, placebo-controlled, randomized study. This safety trial was stopped prematurely when 342 patients (339 valid) had been randomized because of an imbalance in endpoints. Demographic data, cardiovascular risk factors, and BP on admission, on study onset, and within the whole study period were not significantly different between the two groups. However, the cumulative 12-month mortality and the number of vascular events differed significantly in favor of the candesartan cilexetil group (odds ratio [OR]: 0.475, 95% CI: 0.252–0.895).

SCAST
Candesartan for treatment of acute stroke (SCAST) was designed to study whether careful BP lowering treatment with candesartan cilexetil is beneficial in patients with acute stroke and raised BP.[30] 2029 patients were randomly allocated to treatment groups (1017 candesartan cilexetil, 1012 placebo), within 30 hours of stroke onset, for 7 days, with doses increasing from 4 mg on day 1 to 16 mg on days 3–7. During the 7-day treatment period, BP was significantly lower in patients allocated candesartan cilexetil than in those on placebo (mean 147/82 mmHg in the candesartan cilexetil group on day 7 vs 152/84 mmHg in the placebo group, $P < 0.0001$). During 6 months' follow-up, the risk of the composite vascular endpoint did not differ between treatment groups (candesartan cilexetil 120 events vs placebo 111 events, adjusted hazard ratio [HR]: 1.09, 95% CI: 0.84–1.41, $P = 0.52$). Analysis of functional outcome suggested a higher risk of poor outcome in the candesartan cilexetil group (adjusted common OR: 1.17, 95% CI: 1.00–1.38, $P = 0.048$ [not significant at $P \leq 0.025$ level]). The observed effects were similar for all prespecified secondary endpoints (including death from any cause, vascular death, ischemic stroke, hemorrhagic stroke, myocardial infarction, stroke progression, symptomatic hypotension, and renal failure)

and outcomes, and there was no evidence of a differential effect in any of the prespecified subgroups. During follow-up, nine (1%) patients on candesartan cilexetil and five (<1%) on placebo had symptomatic hypotension, and renal failure was reported for 18 (2%) patients taking candesartan cilexetil and 13 (1%) allocated placebo.

Retinopathy
DIRECT-Prevent 1 and DIRECT-Protect 1
DIabetic REtinopathy Candesartan Trials (DIRECT) assessed the effect of candesartan cilexetil on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes.[31] Participants aged 18–55 years, with normotensive, normoalbuminuric type 1 diabetes without retinopathy were recruited to the DIRECT-Prevent 1 trial (n = 710 candesartan cilexetil/710 placebo) and those with existing retinopathy were recruited to DIRECT-Protect 1 (n = 1905 candesartan cilexetil/954 placebo), and prospectively randomized to candesartan 16 mg once a day or matching placebo. After 1 month, the dose was doubled to 32 mg. The primary endpoints were incidence and progression of retinopathy and were defined as at least a two-step and at least a three-step increase on the Early Treatment Diabetic Retinopathy Study scale, respectively. Incidence of retinopathy was seen in 178 (25%) participants in the candesartan cilexetil group versus 217 (31%) in the placebo group. Progression of retinopathy occurred in 127 (13%) participants in the candesartan cilexetil group versus 124 (13%) in the placebo group. HR for candesartan cilexetil versus placebo was 0.82 (95% CI: 0.67–1.00, $P = 0.0508$) for incidence of retinopathy and 1.02 (95% CI: 0.80–1.31, $P = 0.85$) for progression of retinopathy. The post-hoc outcome of at least a three-step increase for incidence yielded an HR of 0.65 (95% CI: 0.48–0.87, $P = 0.0034$), which was attenuated but still significant after adjustment for baseline characteristics (0.71, 95% CI: 0.53–0.95, $P = 0.046$). Final Early Treatment Diabetic Retinopathy Study scale level was more likely to have improved with candesartan cilexetil treatment in both DIRECT-Prevent 1 (OR: 1.16, 95% CI: 1.05–1.30, $P = 0.0048$) and DIRECT-Protect 1 (1.12, 95% CI: 1.01–1.25, $P = 0.0264$).

DIRECT-Protect 2
DIRECT-Protect 2 evaluated the effect of candesartan cilexetil on progression and regression of retinopathy in type 2 diabetes.[32] 1905 normoalbuminuric, normotensive, or treated hypertensive participants (aged 37–75 years) with type 2 diabetes with mild to moderately severe retinopathy

were randomized to candesartan cilexetil 16 mg once a day (n = 951) or placebo (n = 954). After 1 month, the dose was doubled to 32 mg once per day. Progression of retinopathy was the primary endpoint, and regression was a secondary endpoint. 161 (17%) patients in the candesartan cilexetil group and 182 (19%) in the placebo group had progression of retinopathy by three steps or more on the Early Treatment Diabetic Retinopathy Study scale. The risk of progression of retinopathy was nonsignificantly reduced by 13% in patients on candesartan cilexetil compared with those on placebo (HR: 0.87, 95% CI: 0.70–1.08, $P = 0.20$). Regression on active treatment was increased by 34% (HR: 1.34, 95% CI: 1.08–1.68, $P = 0.009$). HRs were not attenuated by adjustment for baseline risk factors or changes in BP during the trial. An overall change towards less severe retinopathy by the end of the trial was observed in the candesartan cilexetil group (OR: 1.17, 95% CI: 1.05–1.30, $P = 0.003$). Adverse events did not differ between the treatment groups.

New-onset diabetes prevention
CASE-J trial
The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial was a prospective, randomized, open-label study designed to compare the long-term effects of candesartan cilexetil and amlodipine on the incidence of cardiovascular events, represented as a composite of sudden death and cerebrovascular, cardiac, renal, and vascular events in high-risk Japanese hypertensive patients.[33,34] 4728 patients (mean age 63.8 years; mean body mass index [BMI] 24.6 kg/m^2) were followed for an average of 3.2 years. The role of pre-existing diabetes or obesity on these outcomes were subanalyzed using a multivariate Cox regression model. BP was well controlled with both treatment-based regimens (136.1/77.3 mmHg for candesartan cilexetil-based regimens and 134.4/76.7 mmHg for amlodipine-based regimens after 3 years). Primary cardiovascular events occurred in 134 patients with both the candesartan cilexetil- and amlodipine-based regimens. The two treatment-based regimens produced no significant differences in cardiovascular morbidity or mortality in all high-risk Japanese hypertensive patients (HR: 1.01, 95% CI: 0.79–1.28, $P = 0.969$), but all-cause mortality was significantly higher with amlodipine than with candesartan cilexetil among patients with BMI $\geq$ 27.5 kg/m^2 (adjusted HR: 0.32, range: 0.13–0.75, $P = 0.009$). New-onset diabetes occurred in fewer patients taking candesartan cilexetil (8.7/1000 person-years) than in those taking amlodipine (13.6/1000 person-years), which resulted in a 36% relative

risk reduction (HR: 0.64, 95% CI: 0.43–0.97, $P = 0.033$). Moreover, the increase in new-onset diabetes was dependent on BMI among patients receiving amlodipine, whereas no such dependency was noticed for candesartan cilexetil (interaction $P = 0.016$). Candesartan cilexetil treatment may reduce all-cause death and decrease the incidence of new-onset diabetes in obese patients.

Migraine

Candesartan cilexetil was evaluated in a prospective, randomized, double-blind, crossover study in 60 patients with migraine.[35] Candesartan cilexetil 16 mg per day was found to reduce the mean number of days with headache and migraine compared with placebo (13.6 vs 18.5 days, respectively, with headache [$P = 0.001$]; 9.0 vs 12.6 days, respectively, with migraine [$P < 0.001$]). Candesartan cilexetil also appeared to significantly decrease headache severity, level of disability, and days of sick leave due to headache. The rate of response to candesartan cilexetil, based on a 50 percent or more reduction in the number of days with migraine, was 40.4%, compared with 3.5% for placebo ($P < 0.001$). Adverse effects with candesartan cilexetil were similar to those with placebo.

Atrial fibrillation
J-RHYTHM II

The Japanese Rhythm management trial II for atrial fibrillation (J-RHYTHM II study) is an open-label randomized comparison between an ARB (candesartan cilexetil) and a calcium channel blocker (CCB) (amlodipine) in the treatment of paroxysmal atrial fibrillation associated with hypertension.[36] Using daily transtelephonic monitoring, we examined asymptomatic and symptomatic paroxysmal atrial fibrillation episodes during a maximum 1 year treatment. The primary endpoint was the difference in atrial fibrillation frequency between the pretreatment period and the final month of the follow-up. The secondary endpoints included cardiovascular events, development of persistent atrial fibrillation, left atrial dimension, and quality-of-life (QOL). The study enrolled 318 patients (aged 66 years, male/female 219/99, 158 in the ARB group and 160 in the CCB group) treated at 48 sites throughout Japan. At baseline, the frequency of atrial fibrillation episodes (days/month) was 3.8 ± 5.0 in the ARB group versus 4.8 ± 6.3 in the CCB group (not significant). During the follow-up, BP was significantly lower in the CCB group than in the ARB group ($P < 0.001$). The atrial fibrillation frequency decreased similarly in both groups, and there was no significant difference in the primary

endpoint between the two groups. There were no significant differences between the two groups in the development of persistent atrial fibrillation, changes in left atrial dimension, occurrence of cardiovascular events, or changes in QOL.

Comparative safety and tolerability

Candesartan cilexetil as other ARBS is generally well tolerated and the incidence of discontinuation is comparable with that of placebo. Candesartan cilexetil does not cause cough and the incidence of angioedema is low. In patients whose BP is highly dependent on the renin-angiotensin system candesartan cilexetil can cause hypotension, oliguria, renal failure, and hyperkalemia. Candesartan cilexetil should be used cautiously in patients with renal failure who are taking potassium supplements or spironolactone to avoid hyperkalemia. The dose of candesartan cilexetil must be adjusted when it is administered along with other antihypertensive drugs to prevent hypotension.[37–42]

Many of the hypertensive patients have not responded adequately to candesartan cilexetil alone. Administration of α-blockers, β-blockers, diuretics, and calcium antagonists along with candesartan cilexetil is safe and effective.[16–18,33,34]

ARBs are known to cause fetal malformations and neonatal problems if administered during pregnancy and this can prove an impediment to their use in women of child-bearing potential. The teratogenic potential of RAS-inhibiting/blocking agents administered during the second and third trimesters of pregnancy is well established. Abnormalities reported include fetal craniofacial abnormalities and limb contractures, probably consequent to oligohydramnious and failed renal development. An interesting report checked teratogenity of candesartan cilexetil in the first trimester. 615 (43.3%), 813 (42.7%), and 957 (50.2%) women were randomized to either candesartan cilexetil 32 mg once daily, or placebo in DIRECT-Prevent 1, DIRECT-Protect 1 and DIRECT-Protect 2, respectively. Of the women who were randomized and took at least one dose of study drug, 178 patients (73 from Prevent 1 and 105 from Protect (1) became pregnant (86 from the candesartan cilexetil and 92 from the placebo groups). Delivery outcomes were similar for the candesartan cilexetil and placebo groups: full term delivery (51 candesartan cilexetil, 50 placebo), premature birth (21 candesartan cilexetil, 27 placebo), spontaneous miscarriage (12 candesartan cilexetil, 15 placebo), elective termination (15 candesartan cilexetil, 14 placebo), and other (1 candesartan cilexetil, 2 placebo). Most infants were healthy, whether full term or premature. There were two stillbirths in the candesartan cilexetil group and one in

the placebo group, and two 'sick babies' in the candesartan cilexetil group and eight in the placebo group. The only congenital malformation reported was a ventricular septal defect in the placebo group. The DIRECT experience indicates that exposure to a relatively high dosage of candesartan cilexetil, 32 mg/day, for up to 8 weeks into the first trimester of pregnancy may not result in a higher rate of malformations than placebo in normotensive normoalbuminuric women with type 1 diabetes.[31,32,41]

Candesartan cilexetil therapy was generally well tolerated in clinical studies in children and adolescents with hypertension. The pharmacokinetic profile was independent of age, sex, and weight, and was similar to that in adults.[42,43]

Candesartan cilexetil and four other ARBS were assessed for the incidence of cancer in 15 large parallel long-term multicenter double blind clinical trials involving 138,769 participants. The four candesartan cilexetil trials were CHARM, DIRECT 1, SCOPE, and TROPHY. The CHARM Overall program consisted of three separate trials in heart failure patients, including CHARM-Added, CHARM-Alternative and CHARM-Preserved. In CHARM Overall, 6.8% of patients had preexisting cancers at baseline. There was no significant difference in cancer incidence between active and control treatment in any of the individual trials, except for the DIRECT trials in which the cancer incidence was 1.80% in patients randomized to candesartan cilexetil and 1.07% in patients on control treatment (OR: 1.69, 95% CI: 1.06–2.71) From this meta-analysis on 138,679 patients in the 15 major trials of the five ARBs, there was no significant excess in cancer incidence with ARB treatment compared to controls with any individual ARB and overall. Moreover, including CHARM together with the entire previous candesartan cilexetil placebo-controlled trial experience, no consistent differences in fatal and nonfatal neoplasms at different sites have been noted between candesartan cilexetil and placebo. There was no excess of common cancers, ie, lung, prostrate, or breast.[16–19,28,44]

Conclusion

Candesartan cilexetil is an effective antihypertensive agent with a tolerability profile similar to that of placebo. Comparative data indicate that candesartan cilexetil has antihypertensive efficacy as good as or better than that of other major ARBS and has a long duration of action. Regression of left ventricular hypertrophy has been seen with candesartan cilexetil treatment in patients with hypertension. Therefore, candesartan cilexetil is a useful therapeutic option in the management of patients with hypertension and heart failure. Candesartan cilexetil has also been proven to be effective in the prevention and progression of renal disease, retinal disease, and stroke.

Disclosure

The authors report no conflicts of interest in this work.

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