Effect of candesartan cilexetil on diabetic and non-diabetic hypertensive patients: meta-analysis of five randomized double-blind clinical trials

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Objective: To study the effect of candesartan cilexetil (CC) in the management of blood pressure (BP) in diabetic and non-diabetic hypertensive patients.

Methods: A selection of five randomized double-blind clinical trials in which patients were treated for hypertension with CC was analyzed. All of these were similar in design: i) a 4-week placebo run-in period, ii) a 4- to 6-week period (V1) with CC 8 mg once daily (od), after which the dosage was doubled if BP was not normalized (BP >140/90 or BP >130/80 mmHg in diabetes), and iii) a 4- to 6-week period (V2) with CC 8 or 16 mg od. Efficacy was measured at V1 and V2.

Results: 702 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 non-diabetic (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 non-diabetic 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 non-diabetic patients ($p < 0.001$), and to a lesser degree on DBP values ($p = 0.034$).

Conclusions: CC was effective in lowering BP in diabetic and non-diabetic hypertensive patients. CC is a promising therapy to manage hypertensive diabetic patients, as demonstrated by the significant BP reduction.

Keywords: candesartan cilexetil, hypertension, antihypertensive diabetes, blood pressure lowering, angiotensin II receptor antagonist

Short abstract: The effect of candesartan cilexetil (CC) on controlling blood pressure (BP) in hypertensive diabetic and non-diabetic patients was analyzed. Five randomized double-blind trials were pooled treating hypertension by CC (n = 702), including 153 diabetic (21.8%) and 549 non-diabetic (78.2%) patients. After treatment with CC (8–16 mg), significant reductions in SBP, DBP, and pulse pressure (PP) values were observed after 4–6 weeks ($p < 0.001$) and after 8–12 weeks ($p < 0.001$) compared with baseline for all hypertensive patients. Mean BP reductions after 8–12 weeks were higher in diabetic patients than non-diabetic ($p < 0.001$). CC is a promising therapy to treat hypertensive patients, both diabetic and non-diabetic.

Introduction

Essential hypertension is the most prevalent cardiovascular disease in the world, and a major public health issue. Its prevalence is increasing in the adult population, and is estimated to be 30% in developed countries (Asmar et al 2001; Guidelines Committee 2003). Arterial hypertension, in which insulin resistance is common, is strongly associated with type 2 diabetes. Diabetes mellitus is increasing rapidly worldwide, and since many patients with hypertension develop diabetes, this combination of risk factors will account for a large proportion of cardiovascular morbidity and mortality (HDSG 1993; Stamler et al 1993).

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International Guidelines for the Management of Hypertension have emphasized that blood pressure (BP)-lowering therapy can reduce macrovascular disease for diabetic patients which may be more significant than blood glucose control (Staessen et al 1997). Results from different studies (Hansson et al 1998; UKPDS 33 1998; UKPDS 34 1998; UKPDS 38 1998) have demonstrated that aggressive lowering of diastolic BP (DPB) in diabetic patients was accompanied by reductions of macrovascular and microvascular events. In addition, the aggressive antihypertensive treatment of diabetic patients with systolic hypertension has been favored in some studies (SHEP Cooperative Research Group 1991; Bakris et al 2000; Chaudhry et al 2004).

Pharmacological agents recommended as initial therapy for diabetic patients include diuretics, β-blockers, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and angiotensin II blocker receptors (ARBs) (Guidelines Subcommittee 1999; Chobanian et al 2003). The choice of antihypertensive drug regimen in diabetic subjects is important for several reasons: they are susceptible to suffer metabolic decompensation, and the diabetic state may alter the pharmacokinetics of several cardiovascular drugs (Preston et al 2001). In this way, captopril was found superior to a diuretic/β-blocker antihypertensive treatment in diabetic patients, especially in those with metabolic decompensation (Niskanen et al 2001). Consequently, dosage requirements established for non-diabetic patients, when applied to the patient with diabetes, may potentially result in either therapeutic failure or undesirable adverse effects. Some epidemiological and clinical studies suggested a causal link between the use of thiazide diuretics and the subsequent development of type 2 diabetes (Bengtsson et al 1984; Padwal and Laupacis 2004), and β-blockers are not specifically indicated in diabetic patients (Scheen 2004). ACE inhibitors (Trost and Weidman 1987; Pollare et al 1989; Berne et al 1991; Oksa et al 1994; Padwal and Laupacis 2004; Scheen 2004) and calcium channel antagonists (Trost and Weidmann 1987; Padwal and Laupacis 2004; Scheen 2004) have little or no significant effects on plasma glucose and insulin levels in patients with and without diabetes.

ARBs have beneficial renal effects in patients with diabetes and nephropathy (Brenner et al 2001; Lewis et al 2001; Parving et al 2001; Lindholm et al 2002). A recent study demonstrated that a subset of angiotensin receptor antagonists (ARAs) induces peroxisome proliferators-activated receptor (PPARγ), providing a potential mechanism for their insulin-sensitizing/antidiabetic effects (Scheen 2004) and an opportunity for the prevention and treatment of diabetes and cardiovascular disease in high-risk populations (Pershadsingh and Kurtz 2004). Among the ARBs, candesartan cilexetil (CC) is a potent, highly selective, angiotensin II type 1 (AT1) blocker receptor. Due to tight binding to and slow dissociation from the receptor, CC provides a strong, dose-dependent, and long-lasting antihypertensive effect. CC does not affect glucose homeostasis or the serum lipid profile (Trenwalder et al 1998), and is effective in reducing BP and microalbuminuria (Mogensen et al 2000) in hypertensive patients with type 2 diabetes. Five randomized double-blind studies (Denolle et al 2001; Imbs and Nisse-Durgeat 2005; Baguet et al 2006; Olivier JP, pers comm; Baguet JP, pers comm) demonstrated the efficacy of CC (8–16 mg) in controlling hypertensive patients. Whether this efficacy is similar in diabetic and non-diabetic patients is not yet established. The aim of this study was to analyze the effect of CC on BP in these two populations by pooling data from five randomized double-blind clinical trials (Denolle et al 2001; Imbs and Nisse-Durgeat 2005; Baguet et al 2006; Olivier JP, pers comm; Baguet JP, pers comm).

Materials and methods

Study population

This was a retrospective data meta-analysis of five randomized double-blind studies (Trenkwalder et al 1998; Mogensen et al 2000; Imbs and Nisse-Durgeat 2005; Baguet JP, pers comm; Olivier JP, pers comm) evaluating the efficacy of CC (8–16 mg). These five studies had a similar design: 2- to 4-week placebo wash out period, followed by 4- to 6-week double-blind period where patients received the active drug once daily. After this period, if BP was not normalized (SBP or DBP ≥140/90 mmHg or ≥130/80 mmHg in diabetes patients) the treatment could be doubled during another 4- to 6-week period. Efficacy was analyzed at V1 (after the first CC period treatment) and at V2 (after the second period treatment). A total of 702 patients treated by CC were included in this analysis.

Statistical analysis

All statistical analysis was undertaken using a Number Cruncher Statistical System (NCSS 2000, Kaysville, Utah, USA). Quantitative variables were expressed as mean ± SD, minimum and upper values, and were compared using a Student's t-test; a Wilcoxon test was performed if the data

were not normally distributed. Qualitative variables were expressed as absolute number and percentage values, and were analyzed using a Chi-square test.

Mean pressure values were compared before and after CC treatment in each group, and between groups (diabetic and non-diabetic patients) using a t-test. Final blood pressure (V1 and V2) comparison between diabetic and non-diabetic group was performed by a covariance analysis with and adjustment to the initial BP values and weight. $P < 0.05$ was considered statistically significant.

Results

Patients

The patient characteristics are presented in Table 1. This analysis included 702 hypertensive patients composed of two sub-groups: 153 of diabetic patients (21.8%) and 549 of non-diabetic patients (78.2%). Patients were principally men (57%), with 60 ± 11 years of age. Diabetic patients had higher weight values than non-diabetic patients. At baseline, systolic and diastolic blood pressure values were significantly higher in non-diabetic patients compared with diabetic (Table 1).

Antihypertensive effect of candesartan cilexetil

Blood pressure reduction in overall population

Changes of SBP, DBP, and pulse pressure (PP) values after CC treatment for all patients are shown in Figure 1. Blood pressure values showed a significant decrease at V1 and V2 following CC 8–16 mg treatments. In the global population significant reductions at V1 ($p < 0.001$) and V2 ($p < 0.001$) were found for SBP, DBP, and PP (Figure 1a). The most important change occurred between baseline and V1 (SBP/DBP/PP: –14/–9/–5 mmHg), but the BP values continued to decrease up to V2 (SBP/DBP/PP: –18/–10/–7 mmHg), reaching final BP values of 141/83/58 mmHg for SBP, DBP, and PP respectively (Figure 1a). Mean changes in heart rate were not significant at V1 (–0.2 bpm) or at V2 (–1.1 bpm), reaching a final value of 72 bpm.

Blood pressure reduction in diabetic patients

In diabetic patients, significant reductions at V1 ($p < 0.001$) and V2 ($p < 0.001$) were found for SBP, DBP, and PP (Figure 1b). The most important change occurred between baseline and V1 (SBP/DBP/PP: –14/–9/–5 mmHg), but the BP values continued to decrease up to V2 (SBP/DBP/PP: –21/–11/–10 mmHg), reaching final BP values of 137/82/55 mmHg for SBP, DBP, and PP respectively (Figure 1b). Mean changes in heart rate were not significant at V1 (–0.3 bpm) or at V2 (–1.3 bpm), reaching a final value of 73 bpm.

Blood pressure reduction in non-diabetic patients

In non-diabetic patients, significant reductions at V1 ($p < 0.001$) and V2 ($p < 0.001$) were found for SBP, DBP, and PP (Figure 1c), with the most important change between baseline and V1 (SBP/DBP/PP: –14/–9/–5 mmHg), and a less pronounced decrease up to V2 (SBP/DBP/PP: –17/–11/–7 mmHg), reaching final BP values of 143/84/59 mmHg for SBP, DBP, and PP respectively (Figure 1c). Mean changes in heart rate were not significant at V1 (–0.2 bpm) or at V2 (–1 bpm), reaching a final value of 72 bpm.

Comparison of antihypertensive effect of CC in diabetic and non-diabetic patients

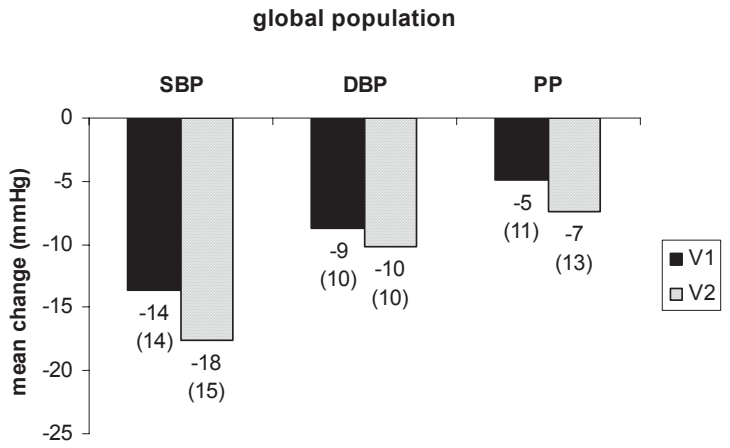
Table 2 compares mean changes of BP and heart rate values between diabetic and non-diabetic patients. At V1, the reductions observed in BP and heart rate values compared with baseline were similar for both diabetic and non-diabetic patients. At V2, the reductions observed in BP values

Table 1 Baseline characteristics of patients

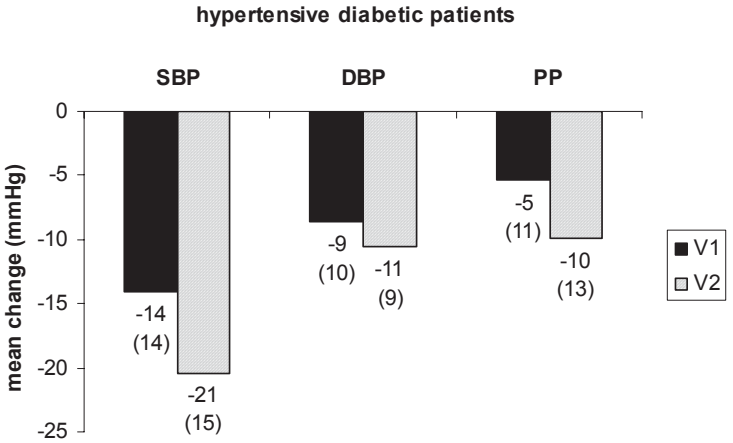
	Diabetic n = 153	Non-diabetic n = 549	Total n = 702	P values
Age, years	60 ± 9	60 ± 12	60 ± 11	NS
Male, n (%)	88 (57.5)	309 (56.3)	397 (56.6)	NS
Weight, kg	84 ± 17	75 ± 15	77 ± 15	<0.001
Height, cm	165 ± 8	167 ± 9	167 ± 9	NS
Systolic BP, mmHg	158 ± 13	160 ± 13	160 ± 13	0.03
Diastolic BP, mmHg	92 ± 9	95 ± 10	94 ± 10	<0.001
Pulse pressure, mmHg	66 ± 13	65 ± 14	65 ± 14	NS
Heart rate, bpm	75 ± 10	73 ± 10	73 ± 10	NS

Results are given as mean ± SD.

a)



b)



c)

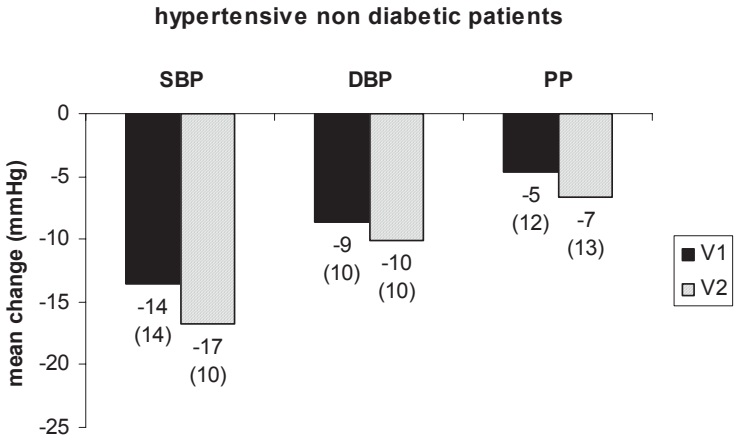


Figure 1 Mean changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) compared with the baseline at V1 (4–6 weeks) and V2 (8–12 weeks) in the global population (a), hypertensive diabetic patients (b), and hypertensive non-diabetic patients (c) treated by CC 8–16 mg. Mean values are given, standard deviation is shown in parentheses.

compared with the baseline were more important in diabetic patients for SBP, DBP and PP values ($p < 0.001$) than in non-diabetic patients (Table 2). The mean changes in heart rate were not statistically significant between diabetic and non-diabetic patients.

Discussion

Previous studies have shown that antihypertensive agents may exert different effects on glycemic control. In general, ACE inhibitors, ARAs, and calcium channel blockers seem to have neutral or beneficial effects, whereas β-blockers and thiazide diuretics tend to worsen insulin resistance for glycemic control (Bengtsson et al 1984; Padwal and Laupacis 2004; Scheen 2004). However, studies have shown conflicting results, even between agents within the same classes (Padwal and Laupacis 2004). Rather than using surrogate blood pressure end points, with different antihypertensive agents, it may be more clinically relevant to examine the effect of the same treatment on controlling hypertensive diabetic and non-diabetic patients. Several trials have been conducted in diabetic patients comparing two or more drugs (Estacio et al 1998; UKPDS 39 1998; HOPE 2000; Lindholm et al 2000, 2002; Mogensen et al 2000; Niskanen et al 2001; Mancia et al 2003), or an active drug against placebo (SHEP Cooperative Research Group 1991; Trenkwalder et al 1998; Lithell et al 2003) but only few studies have evaluated blood pressure lowering using one drug in the same study comparing the effect in diabetic and non-diabetic patients (Jaichenko et al 1998; Preston et al 2001; Gottlieb et al 2003).

The present analysis pooled data of five randomized double-blind clinical trials (Denolle et al 2001; Imbs and Nisse-Durgeat 2005; Baguet et al 2006; Olivier JP, pers comm; Baguet JP, pers comm) with the objective of analyzing the effect of CC on diabetic and non-diabetic patients. The antihypertensive effect of CC 8–16 mg was observed by BP reduction achieved by 12 weeks in all patients treated.

BP values in diabetic hypertensive patients are usually higher than in non-diabetic patients despite the use of larger number of drugs (Estacio et al 1998; Jaichenko et al 1998; UKPDS 39 1998; HOPE 2000; Lindholm et al 2000, 2002; Brenner et al 2001; Lewis et al 2001; Niskanen et al 2001; Parving et al 2001; Gottlieb et al 2003; Lithell et al 2003; Mancia et al 2003). Indeed, treatment is accompanied by large BP reductions, but while achieved DBP is almost invariably well below 90 mmHg and even 80 mmHg, the concomitant SBP remained above 140 mmHg (Brenner et al 2001; Lewis et al 2001; Parving et al 2001; Lindolm et al 2002). Thus, in hypertensive diabetic patients treated with irbesartan 300 mg or amlodipine 10 mg, the final average SBP/DBP values were 140/77 mmHg and 141/77 mmHg respectively (Lewis et al 2001). Irbesartan 150 mg and irbesartan 300 mg administrated to hypertensive diabetic patients with nephropathy gave final SBP/DBP values of 143/83 and 141/83 mmHg, respectively (Parving et al 2001). Hypertensive diabetic patients treated by losartan achieved mean SBP/DBP final values of 140/74 mmHg vs placebo (Brenner et al 2001), and of 146/79 mmHg vs atenolol (Lindolm et al 2002).

In a previous study, CC 8–16 mg lowered SBP/DBP values to 149/89 mmHg compared with 151/90 with placebo (Trenkwalder et al 1998). In the present analysis, a more important reduction in mean SBP, DBP, and PP values was observed in diabetic (137/82/55 mmHg) compared with non-diabetic patients (143/84/59 mmHg).

Table 2 Blood pressure changes in diabetic and non-diabetic hypertensive patients

	Diabetic n = 153		Non-diabetic n = 549		
	Mean ± SD	Mean change ± SD	Mean ± SD	Mean change ± SD	p
V1[a]					
Systolic BP, mmHg	143 ± 17	–14 ± 14	146 ± 16	–14 ± 15	NS
Diastolic BP, mmHg	84 ± 10	–9 ± 10	86 ± 10	–9 ± 10	NS
Pulse pressure, mmHg	59 ± 12	–5 ± 11	60 ± 13	–10 ± 9	NS
Heart Rate, bpm	74 ± 9	–0.3 ± 7	73 ± 9	–0.2 ± 9	NS
V2[b]					
Systolic BP, mmHg	137 ± 15	–21 ± 15	143 ± 15	–17 ± 14	<0.001
Diastolic BP, mmHg	82 ± 9	–11 ± 9	84 ± 10	–10 ± 10	0.034
Pulse pressure, mmHg	55 ± 10	–10 ± 13	60 ± 13	–7 ± 13	<0.001
Heart rate, bpm	73 ± 9	–1.3 ± 7	72 ± 9	–1 ± 9	NS

Mean change values were obtained comparing with the baseline.
[a]V1: 4- to 6-week period of treatment with CC 8 mg once daily.
[b]V2: 8- to 12-week period of treatment with 8–16 mg once daily.

In spite of a good response to CC in BP lowering, the recommendations to lower SBP in diabetic patients to values below 130 mmHg were not totally achieved. The difference in the BP response between diabetic and non-diabetic patients may partly be explained by a physiological mechanisms differently acting in diabetic and non diabetic patients.

Several randomized clinical trials suggested that the inhibition of the renin-angiotensin (RA) system reduces the risk of new onset of type 2 diabetes mellitus (T2DM) in patients with arterial hypertension (Padwal and Laupacis 2004; Scheen 2004) or with congestive heart failure (Padwal and Laupacis 2004). Considering the pandemic of T2DM, such a pharmacological approach deserves further attention among the strategies aiming at preventing the disease. This preventive effect of the RA inhibition should involve the intimate mechanisms of the complex pathophysiology of T2DM. A Japanese study suggested that hypoadiponectinemia is related to insulin resistance in essential hypertension (Furuhashi et al 2003). It also showed that treatment with temocarpil or candesartan significantly decreases blood pressure and increased insulin-mediated glucose disposal and plasma adiponectin concentrations (Furuhashi et al 2003). These observations require further investigation.

Another possible mode of action has been hypothesized for ARBs. A recent study (Mancia and Grassi 2002) demonstrated that a subset of ARAs induces PPAR-γ activity by interaction with the PPAR-γ ligand binding domain. ARAs with PPAR-γ activating properties at low (telmisartan), medium (irbesartan), and very high concentrations (losartan) as well as a non-activating ARA (eposartan) have been identified. The authors concluded that molecules that can simultaneously block the ATII receptor and activate PPAR-γ have the potential to treat both hemodynamic and biochemical features.

CC has been useful in treating hypertensive patients who have experienced side-effects with other antihypertensive agents. Its good tolerability has been reported and favorable effects on target organ damage, morbidity, and mortality were achieved in long-term studies (Lithell et al 2003). The lower rate of new-onset diabetes mellitus reported in the CC group compared with the control group found in SCOPE is of the same magnitude as that observed in the other ARB losartan-treated group compared with the β-blocker treated group in the LIFE study (Lindholm et al 2002). A more favorable metabolic profile and a lower risk of developing diabetes in hypertensive patients treated with CC 16 mg was also described in the ALPINE study (Lindholm et al 2003).

CC has potential as initial treatment of hypertension and, as shown in the present analysis, CC was effective in diabetic as well as in non-diabetic patients, and furthermore, with a significant SBP, DBP, and PP lowering in diabetic patients. CC merits further investigation in diabetic patients.

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