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ORIGINAL RESEARCH ARTICLE

Candesartan Cilexetil 32 mg/Hydrochlorothiazide 25 mg in Unselected Patients with High or Very High Cardiovascular Risk: Efficacy, Safety, and Metabolic Impact

Peter Bramlage · Hartmut Buhck · Claudia Zemmrich

Abstract

Background and Objectives Safety and efficacy of the fixed-dose combination candesartan cilexetil 32 mg/hydrochlorothiazide 25 mg has been demonstrated in a number of randomized clinical trials. Because stringent inclusion and exclusion criteria prohibit many high-risk patients from being investigated in clinical trials we aimed to assess the effectiveness, tolerability, and safety in a large unselected cohort of high-risk patients in primary care. The primary objective was the efficacy of candesartan cilexetil 32 mg/hydrochlorothiazide 25 mg in lowering the office-based blood pressure (BP). Secondary objectives were changes of metabolic parameters and safety.

Methods A multicenter, non-interventional study of patients with a BP $\geq$140 mmHg systolic and/or 90 mmHg diastolic and additional cardiovascular risk factors. Patients received the fixed-dose combination of candesartan cilexetil 32 mg and hydrochlorothiazide 25 mg for 24 weeks.

Results A total of 3,390 patients with a mean age of 61.7 $\pm$ 10.6 years, 57.8 % being male, and a mean body mass index of 29.7 kg/m^2 were documented. Of these, 70.9 % had at least one additional cardiovascular risk factor such as coronary artery disease (45.5 %) or diabetes mellitus (44.5 %). Baseline BP was 159.6 $\pm$ 15.3 over 93.5 $\pm$ 9.5 mmHg. BP at 24 weeks was reduced by 32.3 $\pm$ 15.8 systolic and 16.1 $\pm$ 10.2 mmHg diastolic compared with baseline ($p < 0.001$ each). Systolic BP (SBP) and diastolic BP (DBP) was normalized (<140/<90 mmHg) in 57.4 % of non-diabetic patients. An SBP <140 mmHg or SBP reduction of $\geq$20 mmHg was achieved by 77.9 % non-diabetic patients. Fasting plasma glucose (−5.9 mg/dL), glycosylated hemoglobin (−0.18 %), low-density lipoprotein cholesterol (−8.5 mg/dL) and triglycerides (−20.3 mg/dL) were reduced significantly, high-density lipoprotein was increased by 0.18 %, while potassium and creatinine levels remained stable. The proportion of patients with adverse drug reactions (ADRs) was 1.3 % ($n = 61$ events in 45 patients). There were ten serious ADRs in eight patients; four patients died without causal relationship to study drug.

Conclusions The results confirm previous randomized clinical trial data supporting the effectiveness, tolerability, and safety of this fixed-dose combination in an unselected patient population with high cardiovascular risk.

1 Background

The majority of patients at high or very high cardiovascular risk need antihypertensive combination therapy to achieve blood pressure (BP) targets. Diuretics are used as standard first-line antihypertensive agents and added as preferred initial combination partners in case of insufficient antihypertensive monotherapy. This widely used antihypertensive standard combination regimen was questioned after the ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension) trial results demonstrated a more effective cardiovascular event reduction with a calcium antagonist added to benazepril than with a thiazide diuretic added to

P. Bramlage (✉) · C. Zemmrich
Institut für Pharmakologie und präventive Medizin, Menzelstrasse 21, 15831 Mahlow, Germany
e-mail: peter.bramlage@ippmed.de

C. Zemmrich
e-mail: claudia.zemmrich@ippmed.de

H. Buhck
MedCommTools, Medical-Scientific Consultancy, Hannover, Germany
e-mail: dr.buhck@medcommtools.de

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benazepril. However, this finding was not confirmed in any other randomized trial, and therefore the current European Society of Hypertension guideline 2013 stated that the evidence provided by ACCOMPLISH does not appear to bear sufficient weight to exclude diuretics from first-line choice [1, 2].

Impaired glucose tolerance, worsening of the lipid profile, and decreased potassium levels are known adverse effects of thiazide diuretics, especially in high doses, which are discussed as negatively affecting heart rhythm stability and the overall metabolic situation [3]. The incidence of glucose intolerance under hydrochlorothiazide treatment was found to be 2.9 % in the HAPPHY (Heart Attack Primary Prevention in Hypertension) trial [4]. The underlying mechanism seems to be a disturbed insulin secretion from the Langerhans cells and a peripheral insulin resistance that is mediated by the diuretic and renin-angiotensin-system blockade-induced abnormally low concentration of serum potassium. By combining diuretics with an angiotensin receptor blocker (ARB), the metabolic side effects of diuretics can be counteracted, the excretion of potassium limited, and the insulin secretion improved, qualifying those compounds as ideal combination partners [5–9].

The combination of candesartan cilexetil and hydrochlorothiazide has shown an excellent efficacy and safety profile in clinical trials investigating the frequent clinical situation of patients being inadequately controlled with ARB monotherapy and uptitrated with hydrochlorothiazide as combination partner [10, 11] or with previous insufficient diuretic monotherapy [12, 13].

The primary objective of the present study was to confirm existing clinical trial-derived evidence for a positive efficacy profile of candesartan cilexetil 32 mg/hydrochlorothiazide 25 mg fixed-dose combination (FDC) after 18–24 weeks of intake in a broad spectrum of unselected high cardiovascular risk primary care patients, with a special focus on the impact on the metabolic profile and safety.

2 Methods

This multicenter, open-label, observational non-interventional study was performed at 606 centers (general practitioners, internists, cardiologists) in Germany. Ethical approval was obtained prior to commencement of the study by the "Freiburger Ethik-Kommission International (FEKI)", an ethics committee for international studies located in Freiburg. Written informed consent was obtained prior to study entry from all patients. Follow-up was 18–24 weeks with an optional interim visit after 8–12 weeks.

2.1 Patient Population and Schedule

Patients of at least 18 years with essential hypertension and at high or very high cardiovascular risk according to European Society of Hypertension/European Society of Cardiology (ESH/ESC) risk classification and insufficient BP control (BP >140/90 mmHg) for at least 8 weeks prior to inclusion were considered for participation. Patients with contraindications according to the summary of product characteristics (hypersensitivity against one of the components or against sulphonamide derivates, impaired renal function, resistant hypokalemia, hypercalcemia, hyponatremia and symptomatic hyperuricemia, moderate to severe liver impairment, pregnancy in the second or third trimester) were excluded from study participation. No additional exclusion criteria regarding concomitant medication or restriction of inclusion depending on co-morbidity or other medication was defined. The prescription of additional antihypertensive agents was allowed, as was the discontinuation of other medications, if necessary.

2.2 Documented Parameters

The parameters documented in the study included demographic characteristics [age, sex, bodyweight and height, waist circumference, early onset of a cardiovascular disease in first-degree relatives (men <55 years, women <65 years) and smoking status], cardiovascular diagnoses [diabetes mellitus, coronary heart disease (CHD), previous myocardial infarction (MI)], angina pectoris, coronary revascularization, atrial fibrillation, heart failure, stroke, transitory ischemic attack, renal insufficiency, retinopathy, neuropathy, peripheral artery disease, left ventricular hypertrophy in the ECG or echocardiography, or vascular signs of high risk such as intima-media thickness >0.9 mm or plaque, ankle-brachial index <0.9 or carotid/femoral pulse-wave velocity >12 ms.

Antihypertensive therapy within the 8 weeks prior to study entry and additional antihypertensive and other comedication during the course of the study was recorded.

The following laboratory parameters were collected at baseline and at final visit after 18–24 weeks: fasting and postprandial blood glucose, oral glucose tolerance test, glycosylated hemoglobin (HbA_{1c}), adiponectin, triglycerides, high-density lipoprotein (HDL-C) and low-density lipoprotein cholesterol (LDL-C), high-sensitivity C-reactive protein (hs-CRP), creatinine, potassium, and uric acid.

At each visit the following characteristics of adverse events (AEs) were recorded, if they occurred: description, first occurrence, grade of severity, outcome of events (recovered, improved, unaltered, deteriorated, lethal), likelihood of causal relationship (yes, no). In addition, it was recorded whether they constituted serious AEs (SAE), i.e., events that were fatal or life-threatening, resulted in persistent or significant disability/incapacity, constituted a congenital anomaly/birth defect, required inpatient

hospitalization or prolongation of existing hospitalization, or were medically significant.

2.3 Blood Pressure (BP) Measurement

Office sitting BP and ambulatory BP was recorded with the standard devices available at the physicians' office (manual sphygmomanometers or semi-automated devices) at each visit according to the guidance for BP measuring (sitting patient under resting conditions, repeat measurements) [14]. Ambulatory mean daytime, night-time, and 24-h BP were collected, where applicable, with half-hourly readings during daytime and hourly readings during the night. Furthermore, it was recorded whether patients achieved the pre-defined BP target (below 140/90 mmHg in non-diabetic and below 130/80 mmHg in diabetic patients).

The following parameters were used for BP-related endpoint evaluations: (1) absolute change of systolic (SBP)/diastolic BP (DBP) after at least 18 weeks of treatment; (2) BP target achievement (for thresholds see above); (3) average change in SBP/DBP from baseline to end of follow-up.

2.4 Statistical Analyses

Data were obtained with a validated application on Adobe ColdFusion® MX 6.1 basis and saved on a Microsoft SQL®—Server 2003. Analyses were performed descriptively and interpreted in an exploratory way. Comparisons were made for BP and laboratory values between baseline and final visit using statistic software SPSS® version 18 (SPSS Inc., Chicago, IL, USA). The safety set (SS) included all patients with at least one dose of study medication. The full analysis set (FAS) represented the SS with valid non-missing data of the SBP and DBP at baseline and at least one available post-baseline visit, preferably 18–24 weeks after inclusion. The FAS was used for efficacy analysis.

Qualitative parameters were summarized by means of absolute and percentage numbers within the various categories. Quantitative parameters were summarized by means of standard statistics [i.e. number of non-missing and missing data, mean, standard deviation (SD), lower quartile, median, upper quartile]. A p value and two-sided 95 % confidence intervals were reported for the changes in SBP and DBP. The absolute and relative frequencies of AEs were reported.

3 Results

A total of 3,390 patients were included into the FAS. The safety data comprised three additional patients in whom the treating physician did not obtain informed consent. The mean study duration was 23.3 weeks with an interims analysis after 10 weeks in 87.6 % of all patients. A follow-up duration of at least 18 weeks was documented for 2,662 patients.

3.1 Baseline Characteristics

The mean age of the patients was 61.7 ± 10.6 years; 46.2 % were women, being slightly older than men (mean age 65.0 vs. 61.7 years in men). Mean body mass index (BMI) was 29.7 kg/m^2 without a notable sex difference (men vs. women 29.5 vs. 29.8 kg/m^2). A BMI >30 kg/m^2 was present in 45.9 % of women and 54.1 % of men. For the frequency of BMI categories, further baseline parameters and co-medication, see Table 1. Mean waist circumference was 103.5 ± 15.0 cm, and 31.5 % had a metabolic syndrome. Only one-fifth of the patients (21.7 %) were smokers, with an average of 19 cigarettes per day. Of the patients, 56.3 % had first-degree relatives with a positive history of early cardiovascular diseases before 55/65 years of age (men/women). The most frequent cardiovascular co-morbidity conditions were CHD (45.5 %), diabetes (44.5 %), and heart failure (23.7 %). 23.1 % had experienced a prior MI, 21.8 % angina pectoris, and 13.7 % a coronary revascularization (for other co-morbidities, see Fig. 1). According to the ESH/ESC criteria, half of the study population (50.4 %) had moderate, 25.0 % severe, and 23.3 % mild hypertension. When joining the study, 1.3 % had a SBP <140 and DBP <90 mmHg.

Almost all patients (98.3 %) had already been treated with antihypertensive drugs before study entry and about half continued antihypertensive co-medication during the course of the study. β-Blockers (30.2 %) and calcium channel blockers (17.5 %) were the most frequently prescribed drug classes (further details are presented at Table 2).

3.2 BP Reduction and Target Achievement

SBP and DBP were reduced by 25.9 ± 15.3 over 12.8 ± 10.0 mmHg with candesartan cilexetil 32 mg/hydrochlorothiazide 25 mg after 8–12 weeks and by 32.3 ± 15.8 over 16.1 ± 10.2 mmHg after 18–24 weeks, respectively, from a mean of 163.6 ± 14.7 over 96.0 ± 9.3 mmHg at baseline ($p < 0.001$ for either value, Fig. 2). No relevant sex difference was demonstrated; the mean absolute SBP/DBP reduction in women was 32.7/15.9 mmHg, and in men was 32.0/16.3 mmHg.

The baseline SBP of patients with a BMI below 25, from 25 to 30, and above 30 kg/m^2, respectively, showed no appreciable difference (163.1 vs. 163.7 vs. 165.9 mmHg), and neither did the amount of BP reduction between patient

groups. Patients with a BMI <25 kg/m^2 had a mean SBP reduction of 34.0 mmHg, compared with 31.9 and 32.7 mmHg in patients with a BMI between 25 and <30 and ≥30 kg/m^2, respectively (see Fig. 3).

Table 1 Patient baseline characteristics

Variable	Value[a]
Age (years) [mean ± SD]	61.7 ± 10.6
Age ≥70 years	1,068 (31.5)
Female	1,567 (42.2)
BMI (kg/m^2) [mean ± SD]	29.7 ± 4.9
>30	1,352 (39.9)
>25–30	1,564 (46.1)
≤25	457 (13.5)
LVH	1,247 (36.8)
Intima-media thickness >0.9 mm	463 (32.4)
ABI <0.9	170 (11.9)
Concomitant medication	
Statins	953 (28.1)
ASA	861 (37.1)
Oral antidiabetic drugs	753 (32.5)
NSAIDs/COX II inhibitors	307 (13.2)
Oral anticoagulants	174 (7.5)
Psychotropic drugs	254 (11.0)

ABI ankle brachial index, *ASA* acetylsalicyl acid, *BMI* body mass index, *COX* cyclo-oxygenase, *LVH* left ventricular hypertrophy, *NSAID* non-steroidal anti-inflammatory drugs, *SD* standard deviation

[a] Values are expressed as *n* (%) unless specified otherwise; missing values not considered in calculated percentages

Table 2 Antihypertensive medication (%) before and during the study

Medication	Before study	At BL	18–24 weeks
Any additional	98.3	47.6	48.6
ACEIs	40.9	3.2	3.0
ARBs	20.0	0.4	0.4
Thiazides	13.1	0.4	0.2
Diuretics	0.1	0.1	0.1
β-Blockers	38.2	29.9	30.2
CCBs	28.7	17.5	17.5
Renin inhibitors	1.2	0.8	0.9
α-Blockers	0.5	0.4	0.4
MRAs	0.0	0.4	0.3

ACEI ACE inhibitor, *ARB* angiotensin receptor blocker, *BL* baseline, *CCB* calcium channel blocker, *MRA* mineralocorticoid receptor antagonist

SBP and DBP targets (≤140/≤90 mmHg in non-diabetic and ≤130/≤80 mmHg in diabetic patients) were achieved in 57.4 % of the non-diabetic and 58.6 % of the diabetic patients, respectively. The target achievement rate increased with the severity of hypertension class, being 53.1/58.0/61.6 % in patients with mild/moderate/severe hypertension. Overall systolic and diastolic response rates (SBP <140 mmHg or >20 mmHg SBP reduction, DBP <90 mmHg or >10 mmHg DBP reduction) were 77.9 and 89.7 %, respectively.

Similar results were observed for ambulatory BP measurement with a first significant reduction between baseline

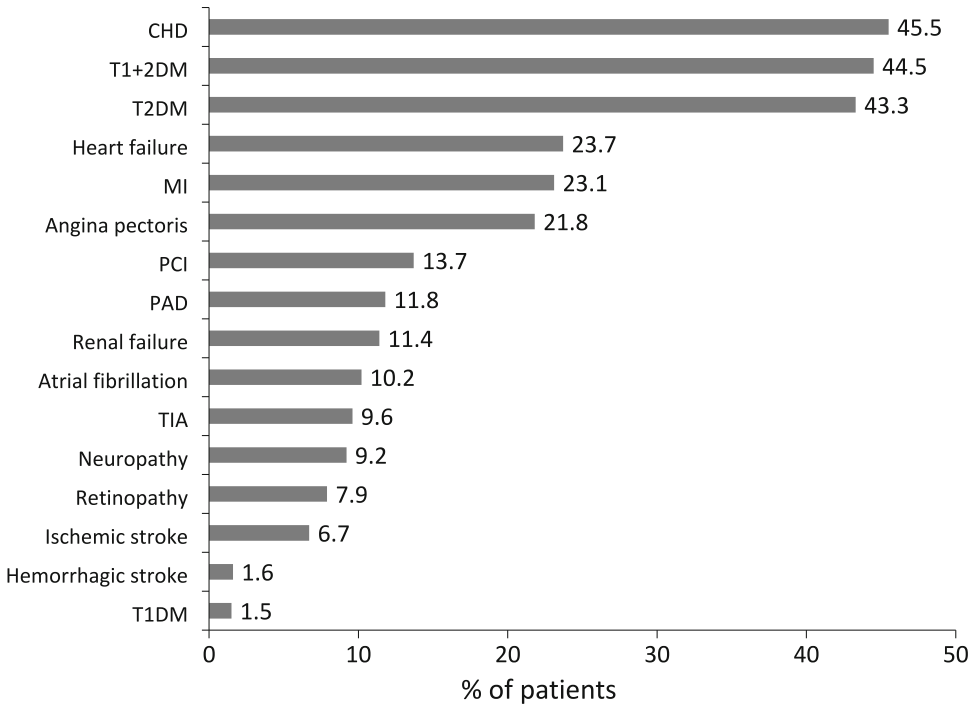

Fig. 1 Co-morbidities of the patient study population present at baseline ($n = 3390$). *CHD* coronary heart disease, *MI* myocardial infarction, *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *TIA* transitory ischemic attack

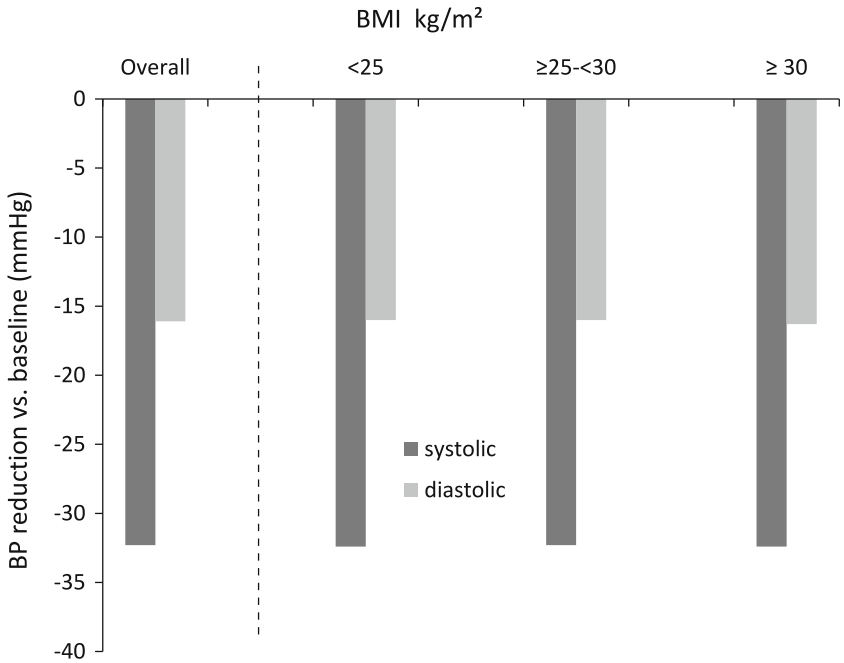

Fig. 2 Mean changes in systolic/diastolic blood pressure between study start and end according to body mass index (kg/m^2). *BMI* body mass index, *BP* blood pressure

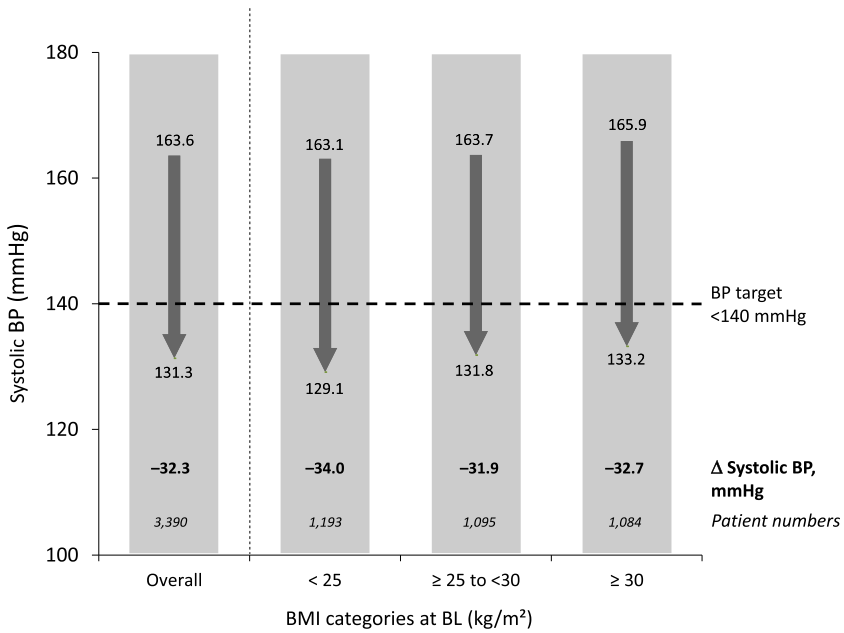

Fig. 3 Absolute systolic blood pressure reduction (mmHg) between baseline and at study end according to baseline BMI. *BMI* body mass index, *BP* blood pressure

and the 10 weeks interim visit and a further reduction to normalized BP values after 23 weeks. Mean 24 h and night-time BP responded accordingly (Fig. 4).

3.3 Metabolic Parameters

Comparing the metabolic risk profile of patients at the start and end of the observation, several parameters improved for the overall study population with numerically higher improvements in patients with a BMI >30 kg/m^2 (in brackets). We observed significant reductions of (1) mean fasting plasma glucose by 5.9 (7.6) mg/dL; (2) HbA_{1c} by 0.18 (0.20) %; (3) triglycerides by 20.3 (23.0) mg/dL; (4) LDL-C by 8.5 (8.5) mg/dL; (5) creatinine by 0.01 (0.03) mg/dL; and (6) an increased HDL-C of +6.7 (14.0) mg/dL [$p < 0.001$ for (1)–(3)]. The glomerular filtration rate, serum potassium, postprandial glucose levels, and uric acid levels remained stable. For all parameters see Table 3.

3.4 Safety and Tolerability

The rate of reported AEs was 1.3 %. Only 61 AEs in 45 patients were recorded, among them ten SAEs in eight

patients. Most frequently named System Organ Classes of the AE's were "cardiac disorders" ($n = 9$), "general disorders and administration site conditions," "gastrointestinal disorders," and "nervous system disorder" ($n = 6$ in each case, respectively). The most frequently named System Organ Class of the SAEs was "cardiac disorders" ($n = 3$). Four SAEs had a fatal outcome, and none of those was considered related to the study drug by the physicians. Three of the ten SAEs were possibly related to study drug, and all affected patients recovered by study end (Table 4).

4 Discussion

Our data support existing clinical trial evidence on the efficacy and safety of candesartan cilexetil 32 mg and hydrochlorothiazide 25 mg as a FDC treatment regimen for a large unselected high cardiovascular risk patient cohort. In contrast to reports from randomized trials about aggravation of metabolic parameters by administering a diuretic, no deterioration of the metabolic situation of the overall and in particular the overweight and obese patient population could be demonstrated.

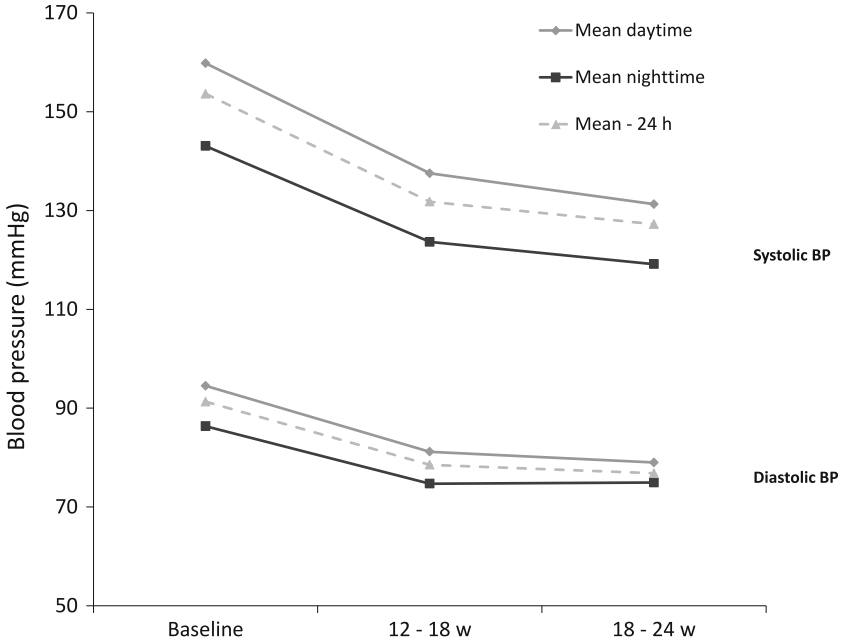

Fig. 4 Ambulatory blood pressure measurement values at baseline, interim visit, and study end. *BP* blood pressure, *h* hours, *w* weeks

Table 3 Metabolic risk factors at study start/end and absolute change within the overall patient population and in patients with a body mass index >30 kg/m^2

Components	Study start	Study end	Change[a]	
			Overall	Patients with BMI >30 kg/m^2
FPG (mg/dL)	110.0 ± 29.6	107.0 ± 26.8	−5.9* ± 23.0	−7.6 ± 23.8
PPG (mg/dL)	154.5 ± 41.7	141.6 ± 33.9	−12.6 ± 24.6	−14.9 ± 26.9
HbA_{1c} (%)	6.5 ± 1.1	6.5 ± 0.9	−0.18* ± 0.68	−0.20 ± 0.69
HDL-C (mg/dL)	53.0 ± 22.0	58.0 ± 138.8	6.7* ± 147.2	14.0 ± 219.1
LDL-C (mg/dL)	134.7 ± 37.5	127.7 ± 33.6	−8.5* ± 27.7	−8.5 ± 28.8
TG (mg/dL)	184.1 ± 97.3	168.5 ± 71.3	−20.3* ± 66.4	−23.0 ± 67.8
Potassium (mmol/L)	4.5 ± 0.65	4.4 ± 0.7	−0.1* ± 0.6	NA
Creatinine (mg/dL)	1.03 ± 0.6	1.0 ± 0.7	−0.01* ± 0.8	−0.03 ± 0.61
GFR (mL/min/1.73 m^2)	76.8 ± 52.6	76.2 ± 29.0	0.8* ± 55.5	−0.4 ± 64.6
Urea (mg/dL)	6.1 ± 1.4	6.1 ± 1.4	−0.1 ± 1.1	NA

Values are expressed as mean ± standard deviation

BMI body mass index, *FPG* fasting plasma glucose, *GFR* glomerular filtration rate, *HbA_{1c}* glycosylated hemoglobin, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *PPG* postprandial glucose, *NA* value not available, *TG* triglycerides

* $p < 0.001$, statistical test applied: Wilcoxon signed ranks test, 2-sided

[a] Absolute values at study start vs. study end

Table 4 Overview of adverse drug events or serious adverse drug events

Variable	*n* (%)
Patients without AE	3,348 (98.7)
Patients with AE	45 (1.3)
Patients with SAEs	8 (0.2)
Fatal SAE	4 (0.1)
Fatal SAE related to study drug	0 (0)
SAE related to study drug	3 (0.1)

AE adverse event, *SAE* serious adverse event

4.1 BP-Lowering Efficacy

A rather consistent BP-lowering effect was recorded with office measurement (−32.3/−16.1 mmHg after 23 weeks) and ambulatory BP measurement (−28.5/−15.5 mmHg), without any notable difference depending on patients' BMI. Our data correspond well with the large amount of existing clinical trials in demonstrating the efficacy of candesartan cilexetil/hydrochlorothiazide combination therapy in different dosage combinations [11, 15–19] and in comparison to other compounds of the same drug class such as losartan [20] and other sartans [21]. Mengden et al. [22] found a similar reduction to 131.7/80.0 mmHg irrespective of prior concomitant medication with a dose of candesartan cilexetil 32 mg/hydrochlorothiazide 12.5 mg or hydrochlorothiazide 25 mg in 4,131 primary care patients with a comparable age profile and baseline BP of 162.1/94.7 mmHg.

Data comparing the antihypertensive efficacy and tolerability of a combination of an ARB and hydrochlorothiazide depending on patients' BMI are available for irbesartan [23], valsartan [8], and losartan [9]. All show the same BMI-independent BP-lowering efficacy and safety, but those trials did not investigate the metabolic effects of this combination in such detail as in the present study. A study comparing metabolic effects of olmesartan and telmisartan observed no difference of the BP reduction achieved at the highest dose with either drug, but an improvement of glycemic control and insulin resistance occurred in the olmesartan group only [24]. Because there was a correlation between the relative changes of HOMAR-IR (Homeostatic Model Assessment–Insulin Resistance; the calculating model for insulin resistance) and hs-CRP, these effects of olmesartan were explained as possibly mediated by an anti-inflammatory drug effect.

4.2 Metabolic Profile/Safety

Candesartan cilexetil/hydrochlorothiazide combination therapy was well-tolerated, as evidenced by the low rate of AEs/SAEs (45 patients with 61 AEs and 8 SAEs, 1.33 %; 3,348 patients without AE/SAE). Those numbers are comparable with previous studies with ARBs and combinations with hydrochlorothiazide [15, 25, 26] that are known to have AE rates similar to placebo.

Significant improvement of metabolic parameters (fasting plasma glucose, cholesterol, triglycerides, HbA_{1c}) was demonstrated in the present study for the overall population and to an even more pronounced degree in obese patients with a BMI $\geq$30 kg/m^2. This adds further evidence to the available data indicating that hydrochlorothiazide can safely be added to candesartan cilexetil without compromising the known favorable metabolic profile of candesartan cilexetil [27–29]. This positive effect of the candesartan cilexetil/hydrochlorothiazide combination therapy is of special importance for patients with diabetes or impaired lipid profile and was proven recently for those high-risk patients by Ketelhut et al. [30] in a study of 4,110 patients with diabetes and microalbuminuria. Like in our study, fasting blood glucose, HbA_{1c}, and lipid parameters (total cholesterol, LDL-C, HDL-C, and triglycerides) were significantly improved ($p < 0.001$). Microalbuminuria, indicative of renal and cardiovascular disease, was significantly reduced by 28.8 % ($p < 0.001$). Tolerability was excellent, with only 16 of 4,110 patients experiencing any AE, of which six were considered to be serious [30].

Lipid values are strongly affected by the presence of statin (HMG-CoA reductase inhibitor) treatment. Only 28 % of the patients indicated statin use at baseline. This is a rather low rate given the fact that 23.1 % of the patients had experienced prior MI and 45.5 % had CHD. It is unlikely, however, that there was a major change in statin use upon enrolment into this observational study, and thus no effect of statins on major metabolic parameters is expected.

4.3 Strengths and limitations

The present study is a real-life trial suffering from all of the typical limitations of non-interventional studies including the lack of a control group, no randomization, potential selection bias, and a less transparent compliance to medication than in randomized clinical trials. Other antihypertensive co-medications and changes of co-therapies during the conduct of the study are not considered, and the baseline situation regarding interfering pre-study antihypertensive medications was not known and therefore not necessarily comparable among all patients.

The BP target in our study was set at 130/80 mmHg, which has been increased recently to 140/90 mmHg also for diabetic patients [31]. This could potentially underestimate our documented target achievement rates when compared with newer data based on the higher targets.

Among the strengths of the study are the better generalizability of the results and transferability into daily medical practice, as unselected patients with a wide range of concomitant diseases and a high cardiovascular risk profile have been included. Those patient groups are typically excluded from clinical trials, but nowadays represent the majority of daily primary care patient populations.

5 Conclusions

The present study demonstrated that the FDC of candesartan cilexetil 32 mg with hydrochlorothiazide 25 mg is an effective modality with an excellent safety profile in unselected high cardiovascular risk patients with previously uncontrolled arterial hypertension independent of the BMI. A 24 ± 2 weeks treatment with candesartan cilexetil 32 mg/hydrochlorothiazide 25 mg led to significant improvements of metabolic parameters such as fasting plasma glucose, HbA_{1c}, and the lipid profile and did not cause any relevant increase of serum potassium or creatinine.

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Conflict of interest PB received consultancy fees, attended advisory boards, and has held lectures for a number of pharmaceutical companies including Takeda. CZ has no conflict of interest to declare. HB is a freelance medical advisor for pharmaceutical companies including Takeda. The study conduct was supported by an unrestricted grant of Takeda Pharma Germany.

Authors' contributions All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data. CZ and PB have drafted the manuscript. The other authors revised the manuscript for important intellectual content and all authors granted final approval of the manuscript to be published.

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