Candesartan cilexetil/hydrochlorothiazide combination treatment versus high-dose candesartan cilexetil monotherapy in patients with mild to moderate cardiovascular risk (CHILI Triple T)

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Background: Candesartan cilexetil has been shown to effectively reduce blood pressure and cardiovascular risk. Whether it is advantageous to combine candesartan cilexetil with low-dose hydrochlorothiazide (HCTZ) or uptitrate it in cases of insufficient blood pressure control has not been fully investigated under routine clinical conditions.

Methods: CHILI Triple T is a prospective, noninterventional, observational study. Patients with uncontrolled hypertension and added cardiovascular risk received a fixed-dose combination of candesartan cilexetil 16 mg and HCTZ 12.5 mg (combination therapy group) or high-dose monotherapy with candesartan cilexetil 32 mg (high-dose monotherapy group).

Results: A total of 4600 patients with a mean age of 63.1 ± 11.0 years, of which 44.7% were female, was included. The combination therapy group had 3337 patients, and the high-dose monotherapy group 1263 patients. Patients in both treatment groups were comparable with respect to age and gender, but patients receiving high-dose monotherapy had a slightly higher mean systolic blood pressure, more prior revascularizations, renal insufficiency, diabetic nephropathy, peripheral artery disease, and a lower ankle brachial index. The use of combination therapy resulted in a blood pressure reduction of $-28.5 \pm 13.8/-14.2 \pm 9.4$ mm Hg ($P < 0.001$ vs $160.2 \pm 13.3/94.5 \pm 8.2$ mm Hg at baseline). The use of high-dose monotherapy reduced blood pressure by $-29.73 \pm 15.3/-14.1 \pm 9.6$ mm Hg ($P < 0.001$ vs $162.4 \pm 14.7/94.7 \pm 8.7$ mm Hg at baseline). Differences in subgroups of patients defined by age, gender, body mass index, dyslipidemia, waist circumference, smoking, prior cardiovascular event, glomerular filtration rate, and microalbuminuria were minor, although partially significant. Tolerability was excellent, with only 28 out of 3358 patients (0.8%) in the combination therapy group and 15 out of 1273 patients (1.2%) in the high-dose monotherapy group experiencing any adverse event, of which one in each group was considered to be serious ($<0.1\%$).

Conclusions: Both the fixed-dose combination of candesartan cilexetil 16 mg and HCTZ 12.5 mg and high-dose monotherapy with candesartan 32 mg were highly effective in lowering blood pressure in patients at increased cardiovascular risk. Tolerability was excellent. The choice of either strategy therefore largely depends on the principal aim: blood pressure reduction with pronounced volume restriction or pronounced additional end-organ protection.

Keywords: essential hypertension, combination therapy, high-dose monotherapy, candesartan cilexetil, noninterventional study, diuretics, Phase IV

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Background

Angiotensin receptor blockers (ARBs) are highly effective at reducing blood pressure in patients with arterial hypertension and have shown to protect against end-organ damage. Candesartan cilexetil is an ARB that has been shown to provide effective blood pressure reduction alone[1–4] or in combination with hydrochlorothiazide (HCTZ).[5–7] Its particular benefit, however, is related not only to its blood pressure-lowering effect but more to its protective effect on end-organs such as the heart,[8–11] kidneys,[12–16] and brain.[17,18] This has usually been achieved in doses up to 32 mg of candesartan cilexetil and is thought to be mediated by effects beyond blood pressure control.[19]

ARBs, including candesartan cilexetil, are frequently used as first-line monotherapy because of their high efficacy, tolerability, and patient compliance. ARB treatment is also an option in patients previously receiving antihypertensive monotherapy with angiotensin-converting enzyme (ACE) inhibitors, β-blockers, or calcium channel blockers, because patients can be safely switched, which results in additional blood pressure lowering.[20] When blood pressure control at low ARB doses is not sufficient, either ARB doses may be increased or combination therapy initiated early.[21] There is, however, no recommendation on the decision to either combine or increase dose, and reports on clinical experience from primary care are sparse.

We therefore designed a noninterventional study in primary care practice asking physicians to document patients at increased cardiovascular risk who had either been prescribed a fixed-dose combination of candesartan cilexetil 16 mg/HCTZ 12.5 mg or a high-dose monotherapy with candesartan 32 mg because blood pressure control under previous antihypertensive pharmacotherapy was insufficient. We chose a noninterventional design to cover the broadest possible patient spectrum and because results of these studies are directly applicable to clinical practice because of the high external validity of this study type.

Patients and methods

CHILI Triple T was a noninterventional, noncontrolled, open-label study with a 12-week follow-up that was conducted with primary care physicians, internists, or diabetologists throughout Germany. The study was registered at the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) and Kassenärztliche Bundesvereinigung (KBV) in accordance with paragraph 67, section 6 of the German Drug Act 2010. Applicable data protection regulations were respected. Participating physicians received remuneration for the documentation of patients in accordance with the Gebührenordnung für Ärzte (GOÄ). Ethical approval was obtained prior to commencement of the study by the Landesärztekammer Thüringen, Jena, Germany, on August 12, 2008. Written informed consent was obtained from all patients.

Patients

Patients aged at least 18 years were eligible for inclusion when a treatment decision to start candesartan 16 mg and HCTZ 12.5 mg or candesartan 32 mg due to arterial hypertension had been made. Further necessary inclusion criteria were uncontrolled blood pressure (≥130/80 mm Hg) on prior antihypertensive therapy for at least 8 weeks, the presence of additional cardiovascular risk factors (eg, diabetes or hyperlipidemia), and compliance with the prescribing information of Blopress® 16 mg Plus or Blopress® 32 mg (both Takeda Pharma GmbH, Aachen, Germany). Physicians were allowed to adjust the dose of any concomitant medication as necessary.

Objective

The objective of this study was to compare the efficacy and safety of a fixed-dose combination treatment strategy (candesartan cilexetil 16 mg and HCTZ 12.5 mg) with high-dose monotherapy (candesartan cilexetil 32 mg). Treatment strategies were to be compared with respect to blood pressure target achievement and blood pressure achievement in patients with different cardiovascular risks at baseline, and to collect data on tolerability and drug safety in the respective treatment group.

Variables

Three visits were scheduled throughout a 12-week follow-up. At the first visit (enrolment), demographic data, body mass index (BMI), cardiovascular risk factors, concomitant disease conditions, previous or concomitant therapies, and a number of laboratory values were documented. At the mandatory second visit, blood pressure readings, blood glucose, antihypertensive pharmacotherapy, and adverse events were documented. At the end of the observation, blood pressure, antihypertensive treatment, and changes in laboratory values were documented. Blood pressure measurements were conducted in agreement with current guidelines after 5 minutes of rest. Treatment satisfaction was monitored as the proportion of physicians indicating patients reaching blood pressure goal and patients' compliance with treatment.

Statistics

The case report forms were collected by the clinical research organization Immedis GmbH, Königswinter, Germany. Case

report forms were checked for consistency and a subset of case report forms verified with the source data (8%). Regarding safety, the trial was adequately sized (n = 4600) to identify rare adverse events, ie, those that may not have been detected in previous clinical studies (incidence 1:1000) with a probability of >95%. The statistical analysis was performed descriptively and was interpreted in an explorative way. Comparisons were made for a number of variables and analyzed using descriptive statistics. The number of patients is given for each value, and differences were calculated in patients with values at baseline and follow-up (per protocol). Data were analyzed with SPSS for Windows, Version 17.02 (SPSS, Inc., Chicago, IL, USA). The tests applied are indicated in the legends of the tables and figures in this article.

Results

Between October 2008 and February 2009 a total of 4600 patients was included (safety population), of which 4527 were analyzed for efficacy. Patients were stratified into two groups according to treatment chosen: 3337 patients received candesartan cilexetil 16 mg in a fixed-dose combination with 12.5 mg HCTZ (combination therapy group), and 1263 patients received candesartan cilexetil 32 mg (monotherapy group).

Patient and clinical characteristics at baseline

Patients had an overall mean age of 63.1 ± 11.0 years, 44.7% were female, and the mean blood pressure at baseline was $160.8 \pm 13.7/94.6 \pm 8.3$ mm Hg (office measurements). Although age and gender were comparable between groups, there was a statistically significant difference with respect to a slightly higher systolic blood pressure at baseline, more prior revascularization procedures, renal insufficiency, diabetic nephropathy, peripheral arterial disease, ankle brachial index < 0.9, and pulse wave velocity > 12 m/s in patients receiving candesartan cilexetil 32 mg (Table 1).

Pharmacotherapy at baseline and during follow-up is illustrated in Table 2. β-blockers, ACE inhibitors, and calcium channel blockers were the most frequently used

Table 1 Baseline characteristics of the study population (U1)

Variables	Candesartan 16 mg + hydrochlorothiazide 12.5 mg		Candesartan 32 mg		*P*-value combination vs monotherapy
	No. of available patient data	%/mean ± SD	No. of available patient data	%/mean ± SD	
Males (%)	1828	54.8	713	56.5	0.288
Age (years)	3328	63.3 ± 11.1	1259	62.8 ± 10.6	0.156
Waist circumference (cm)	2706	102.5 ± 14.0	1002	103.0 ± 15.3	0.388
Smokers (%)	729	21.8	276	21.9	0.953
Blood pressure office measurement					
Systolic (mm Hg)	3336	160 ± 13	1260	162 ± 15	<0.001
Diastolic (mm Hg)	3337	94 ± 8	1259	95 ± 9	0.374
Diabetes (%)	240	7.2	92	7.3	0.792
Concomitant disease (%)					
Coronary artery disease	1296	38.8	505	40.0	0.387
Myocardial infarction	399	12.0	176	13.9	0.065
Angina pectoris	753	22.6	309	24.5	0.151
Prior revascularization	450	13.5	203	16.1	0.018
Heart failure	700	21.0	278	22.0	0.415
Stroke	167	5.0	63	5.0	0.985
Renal insufficiency	268	8.0	152	12.0	<0.001
Diabetic nephropathy	259	7.8	136	10.8	0.001
Diabetic retinopathy	235	7.0	98	7.8	0.402
Peripheral artery disease	406	12.2	187	14.8	0.018
Prior cardiovascular disease in first-grade relatives	1944	58.3	731	57.9	0.868
IMT > 0.9 mm or plaque	505	70.5	235	69.7	0.083
ABI < 0.9	212	29.6	131	38.9	<0.001
PWV > 12 ms	65	9.1	55	16.3	<0.001

Abbreviations: ABI, ankle brachial index; IMT, intima media thickness; PWV, pulse wave velocity; SD, standard deviation.

Table 2 Pharmacotherapy for the treatment of hypertension at baseline (% of patients)

	Candesartan 16 mg + hydrochlorothiazide 12.5 mg		Candesartan 32 mg		P-value combination vs monotherapy
	No. of patients	%	No. of patients	%	
Baseline					
Any (of the 5 groups below)	5264	95.8	2206	95.0	0.113
Angiotensin-converting enzyme inhibitors	1613	29.4	642	27.7	0.128
Angiotensin receptor blockers	425	7.7	217	9.3	0.018
β-blockers	1561	28.4	636	27.4	0.359
Calcium channel blockers	1049	19.1	424	18.3	0.390
Diuretics	616	11.2	287	12.4	0.147
Candesartan 16 mg/hydrochlorothiazide 12.5 mg	5492	100.0	n.a.	n.a.	n.a.
Candesartan 32 mg	n.a.	n.a.	2321	100.0	n.a.
Concomitant pharmacotherapy					
Any (of the 5 groups below)	659	13.4	435	20.3	<0.001
Angiotensin-converting enzyme inhibitors	35	0.7	35	1.6	0.001
Angiotensin receptor blockers*	46	0.9	18	0.8	0.706
β-blockers	235	4.8	102	4.8	0.996
Calcium channel blockers	210	4.3	105	4.9	0.228
Diuretics*	133	2.7	175	8.2	<0.001

Note: *Other than candesartan 32 mg or candesartan 16 mg and hydrochlorothiazide12.5 mg.

drugs at baseline. Either candesartan cilexetil in mono- or combination therapy was added to an existing regimen or prior medication was substituted, resulting in 100% coverage at baseline. Concomitant drug use was low and comparable except for a nominally more frequent use of diuretics in the monotherapy group (8.2% vs 2.7%; $P < 0.001$).

Blood pressure reduction

At baseline, patients had comparable blood pressure values in both treatment arms and in subgroups, defined by the presence of hypertension grade 1–3 (Figure 1). The use of combination therapy resulted in a blood pressure reduction of $-28.5 \pm 13.8/-14.2 \pm 9.4$ mm Hg ($P < 0.001$ with blood pressure of $160.2 \pm 13.3/94.5 \pm 8.2$ mm Hg at baseline).
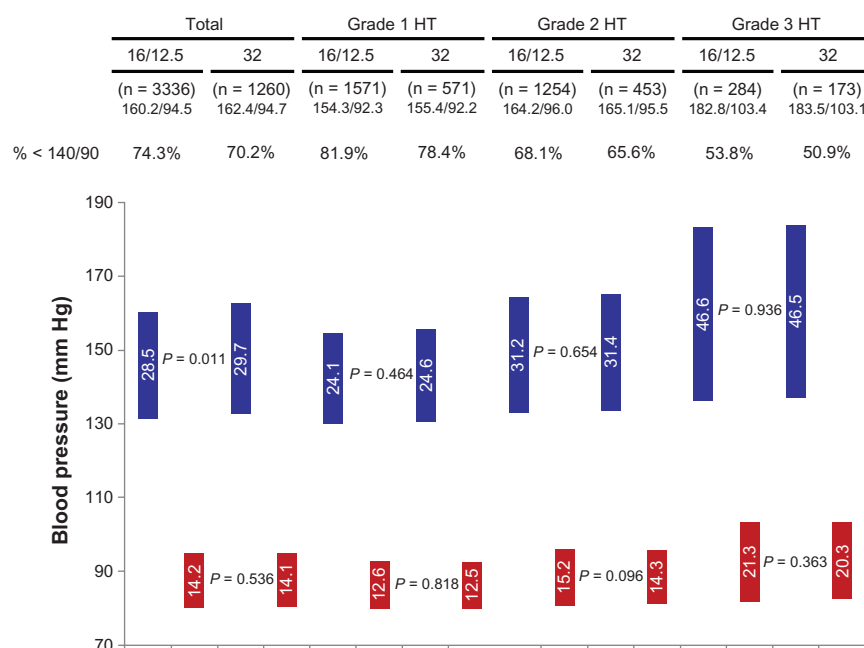

	Total		Grade 1 HT		Grade 2 HT		Grade 3 HT	
	16/12.5	32	16/12.5	32	16/12.5	32	16/12.5	32
	(n = 3336) 160.2/94.5	(n = 1260) 162.4/94.7	(n = 1571) 154.3/92.3	(n = 571) 155.4/92.2	(n = 1254) 164.2/96.0	(n = 453) 165.1/95.5	(n = 284) 182.8/103.4	(n = 173) 183.5/103.1
% < 140/90	74.3%	70.2%	81.9%	78.4%	68.1%	65.6%	53.8%	50.9%

Figure 1 Blood pressure reduction overall and subgroups with grade 1–3 hypertension (HT) 12 weeks after either candesartan cilexetil/hydrochlorothiazide combination (treatment arm 1) or high-dose candesartan monotherapy 32 mg (treatment arm 2). Blood pressure lowering in the total and the subgroups defined by the presence of grade 1, 2, or 3 hypertension was significant ($P < 0.001$, pairwise comparison).

The use of high-dose monotherapy reduced blood pressure by $-29.73 \pm 15.3/-14.1 \pm 9.6$ mm Hg ($P < 0.001$ with blood pressure of $162.4 \pm 14.7/94.7 \pm 8.7$ mm Hg at baseline). Differences were highly significant compared with baseline ($P < 0.0001$) and significant for the difference between systolic blood pressure values ($P = 0.011$). Target blood pressure achievement ($<140/90$ mm Hg) was 74.3% in the combination therapy group and 70.2% in the monotherapy group.

The treatment-induced blood pressure reduction for patient groups, defined by the presence of hypertension grade 1–3 (see mean blood pressure readings at baseline in the respective subgroups), is illustrated in Figure 1. Blood pressure reduction was moderate in grade 1 hypertension

($-24.1/-12.6$ mm Hg combination vs $-24.6/-12.5$ mm Hg monotherapy; both $P < 0.0001$ vs baseline), increased in grade 2 hypertension ($-31.2/-15.2$ vs $-31.4/-14.3$; both $P < 0.0001$ vs baseline), and was strongest in patients with grade 3 hypertension ($-46.6/-21.3$ vs -46.5 vs -20.3; both $P < 0.0001$ vs baseline). The correlation (Pearson 0.754) between blood pressure at baseline and blood pressure reduction was highly significant ($P < 0.001$); differences between mono- and combination therapy were not observed ($P = $ n.s.).

Both patient groups had mostly either high or very high added risk at baseline, defined by blood pressure readings and the presence of comorbid risk factors and disease as
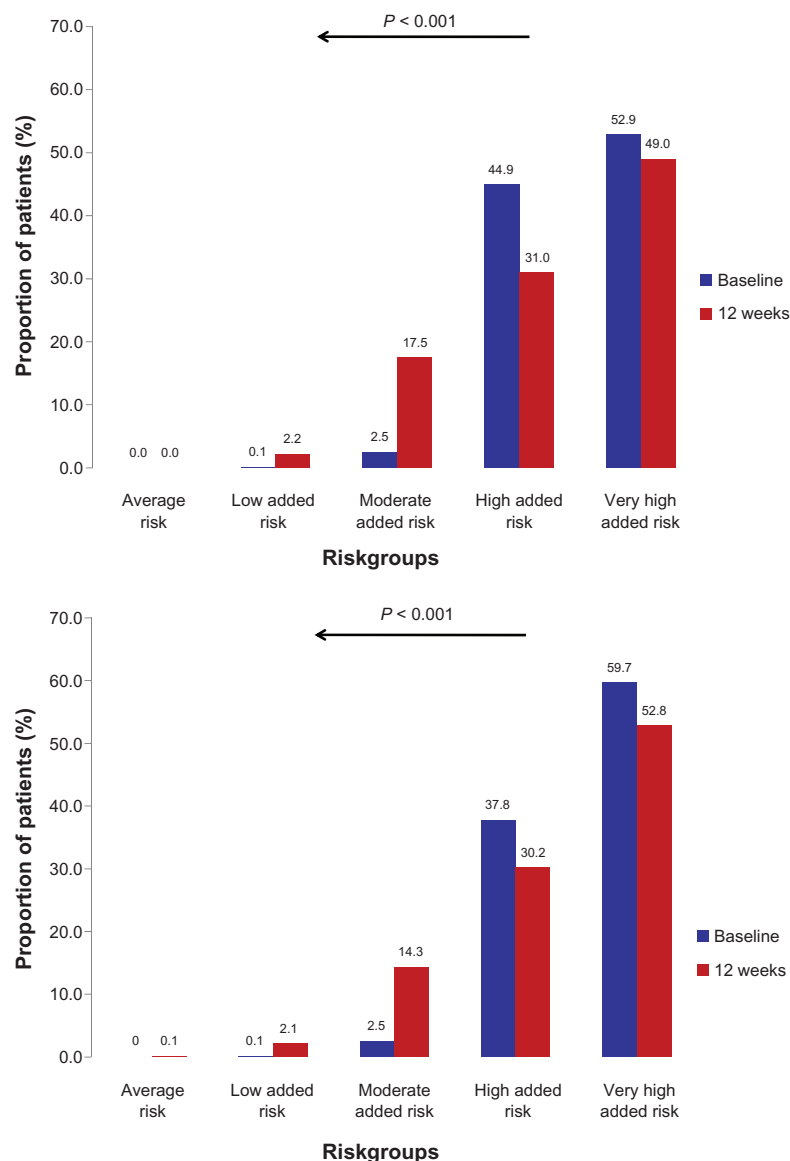

Figure 2 Cardiovascular risk (%) at baseline and after follow-up according to the European Society of Hypertension/European Society of Cardiology 2007 guidelines.[21] **Upper panel:** patients receiving candesartan/hydrochlorothiazide; **Lower panel:** patients receiving candesartan 32 mg. Stratification of cardiovascular risk in five categories. Low, moderate, high, and very high added risk refers to 10-year risk of a cardiovascular fatal or nonfatal event.

outlined in the European Society of Hypertension (ESH)/ European Society of Cardiology (ESC) guidelines (Figure 2, panel A and B).[21] This applied to 44.9% (high) and 52.9% (very high) of patients with the fixed-dose combination, and to 37.8% (high) and 59.7% (very high) in the high-dose monotherapy group. Risk was substantially reduced at the 12-week follow-up ($P < 0.001$ vs baseline in both groups); substantially fewer patients had high or very high added risk, and more patients had low or moderate added risk. Differences between both treatment groups were negligible.

Blood pressure in patient subgroups

The blood pressure reduction in subgroups of patients defined by prior or concomitant antihypertensive pharmacotherapy is displayed in Table 3. Differences compared with baseline were significant ($P < 0.001$), with the least effect observed in patients with prior ARB therapy and those with concomitant use of ACE inhibitors. Pronounced effects were observed in patients with prior β-blocker or diuretic therapy.

Differences between mono- and dual-combination therapy in the respective subgroups were generally in favor of high-dose monotherapy but were significant only for patients for whom a β-blocker was withdrawn ($P = 0.006$).

Blood pressure reductions were further investigated in subgroups of patients defined by age, gender, and BMI (Figure 3; two panels first row), dyslipidemia, waist circumference, and smoking (Figure 3; two panels second row), and prior cardiovascular event, glomerular filtration rate, and the presence of microalbuminuria (Figure 3; two panels last row). Differences were significant for patients aged ≤ 65 years, patients with BMI ≥ 30 kg/m², patients with dyslipidemia, and those who smoke ($P < 0.05$).

Metabolic parameters and tolerability

Twelve weeks after candesartan cilexetil/HCTZ initiation, laboratory values such as glycated hemoglobin, fasting and postprandial glucose, lipids, and renal parameters generally improved, irrespective of whether mono- or combination therapy was employed (Table 4). Differences between treatments

Table 3 Blood pressure reduction versus baseline with respect to prior and concomitant pharmacotherapy for the treatment of hypertension

	Candesartan 16 mg + hydrochlorothiazide 12.5 mg			Candesartan 32 mg			*P*-value Δ combination vs Δ monotherapy
	No. of patients	Blood pressure reduction (mm Hg)	*P*-value vs baseline	No. of patients	Blood pressure reduction (mm Hg)	*P*-value vs baseline	
Prior therapy							
No change of prior therapy	905	28.39	<0.001	373	29.57	<0.001	0.166
Change of prior therapy	2395	28.53	<0.001	865	29.78	<0.001	0.037
Withdrawn therapy							
Angiotensin-converting enzyme inhibitors	1377	28.66	<0.001	494	30.21	<0.001	0.046
Angiotensin receptor blockers	391	25.71	<0.001	190	26.20	<0.001	0.681
β-blockers	327	28.52	<0.001	130	33.06	<0.001	0.006
Calcium channel blockers	342	30.33	<0.001	122	30.34	<0.001	0.996
Diuretics	427	30.40	<0.001	53	32.96	<0.001	0.259
No. of withdrawn drugs							
1 drug withdrawn	1933	28.22	<0.001	745	29.29	<0.001	0.090
≥2 drugs withdrawn	468	29.82	<0.001	121	32.39	<0.001	0.161
Concomitant pharmacotherapy							
Angiotensin-converting enzyme inhibitors	34	27.79	<0.001	34	29.85	<0.001	0.556
Angiotensin receptor blockers	9	30.22	<0.001	3	47.67	0.019	0.099
β-blockers	230	30.71	<0.001	95	29.07	<0.001	0.403
Calcium channel blockers	204	30.39	<0.001	95	29.47	<0.001	0.649
Diuretics	131	29.60	<0.001	150	30.25	<0.001	0.741
No. of concomittant drugs							
No concomitant drugs	2659	28.27	<0.001	908	29.36	<0.001	0.049
1 concomittant drug	1047	28.65	<0.001	350	30.73	<0.001	0.020
≥2 concomittant drugs	2271	28.42	<0.001	899	29.35	<0.001	0.113

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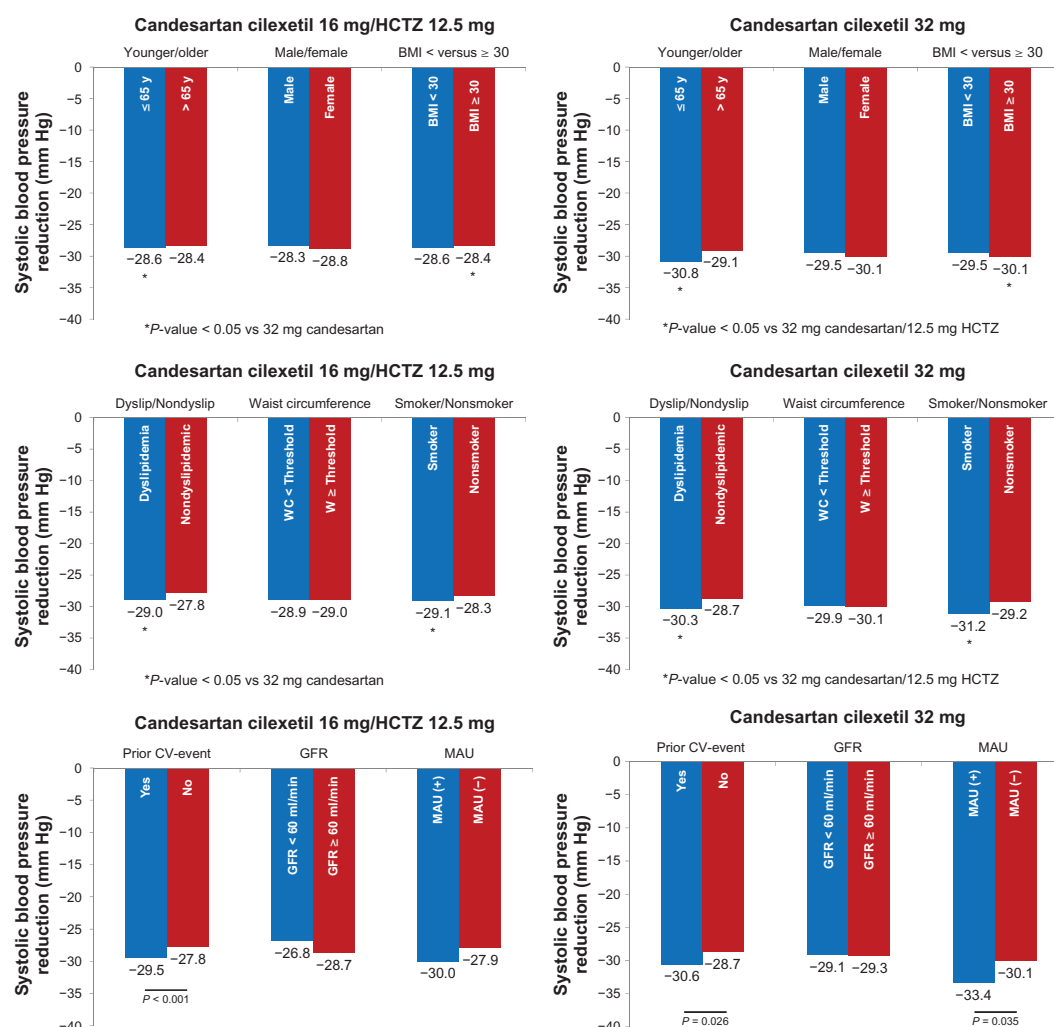
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Figure 3 Systolic blood pressure reduction patient characteristic (age, gender, and BMI: two panels first row), concomitant risk factors (hyperlipidemia, waist circumference, smoking: two panels second row), and end-organ damage (prior CV event, GFR, and MAU: two panels last row).
Notes: *Significant differences are indicated (*P*-value). Other comparisons are not significant.
Abbreviations: BMI, body mass index; CV, cardiovascular; GFR, glomerular filtration rate; HCTZ, hydrochlorothiazide; MAU, microalbuminuria.

were, however, nonsignificant. During the course of the observation, 28 adverse events were reported in patients receiving a fixed-combination treatment (n = 28/3337; 0.8%) and 15 in the monotherapy treatment group (n = 15/1263; 1.2%). One event in each group was considered to be serious. Most adverse events were related to cardiac or vascular disorders. Details are displayed in Table 5 (MedDRA® Primary System Organ Classes, Northrop Grummon Corporation, California, US).

Discussion

Awareness that the majority of patients require two or more antihypertensive agents to reach their blood pressure goal led to the therapeutic concept to introduce combination treatment early, which usually comprises a thiazide diuretic.[21,22] On the other hand, clinical study evidence also suggests that sustainable inhibition of the

renin–angiotensin–aldosterone system (RAAS) at the tissue level, as provided by high-dose monotherapy with an ARB, might afford improved cardiovascular protection beyond pure blood pressure reduction.[19] There is, however, no recommendation on this decision to either combine or increase dose, and reports on clinical experience from primary care are sparse. Therefore, we designed a noninterventional study, the key findings of which are as follows. First, the fixed-dose combination of candesartan cilexetil 16 mg and HCTZ 12.5 mg and high-dose monotherapy with candesartan 32 mg was almost equally effective at lowering blood pressure in patients at increased cardiovascular risk. Blood pressure reduction was enhanced with higher baseline blood pressure. Differences were small in subgroups defined by patients' characteristics, risk factors, and end-organ disease. Second, the degree of added cardiovascular risk, as outlined by the

Table 4 Laboratory values at baseline and during follow-up

	Candesartan 16 mg + hydrochlorothiazide 12.5 mg			Candesartan 32 mg			P-value Δ combination vs Δ monotherapy
	Baseline	12 weeks	Δ vs baseline	Baseline	12 weeks	Δ vs baseline	
Blood glucose							
Fasting blood glucose (mg/dL)	108.8 ± 28.9	103.2 ± 25.8	5.5 ± 18.5	110.5 ± 32.2	106.3 ± 27.5	4.19 ± 23.26	0.257
Postprandial glucose (mg/dL)	147.7 ± 34.9	136.6 ± 32.1	11.1 ± 27.1	148.6 ± 40.3	136.6 ± 37.3	12.0 ± 34.9	0.717
Lipids							
Total cholesterol (mg/dL)	218.2 ± 34.6	205.0 ± 34.5	13.3 ± 29.0	220.4 ± 43.3	210.9 ± 86.7	9.4 ± 86.4	0.351
High-density lipoprotein cholesterol (mg/dL)	51.1 ± 15.2	52.6 ± 16.1	1.50 ± 10.0	52.4 ± 16.6	53.8 ± 19.5	1.4 ± 16.8	0.883
Low-density lipoprotein cholesterol (mg/dL)	131.9 ± 34.9	121.9 ± 30.2	9.95 ± 25.4	135.0 ± 43.9	122.7 ± 32.3	12.3 ± 40.6	0.296
Triglycerides (mg/dL)	187.0 ± 92.7	168.7 ± 71.6	18.3 ± 65.8	189.1 ± 96.2	173.4 ± 112.6	15.7 ± 109.8	0.650
Renal parameters							
Serum-creatinine (mg/dL)	1.55 ± 7.3	1.04 ± 1.5	0.5 ± 7.4	2.3 ± 10.3	1.1 ± 0.7	1.24 ± 10.3	0.157
Glomerular filtration rate (mL/min/1.73 m^2)	71.6 ± 12.2	73.5 ± 22.7	1.90 ± 12.17	64.8 ± 21.4	67.4 ± 22.4	2.6 ± 13.9	0.664
Albuminuria (mg/24 h)	76.5 ± 213.0	46.7 ± 87.8	30.7 ± 172.8	123.6 ± 253.1	84.2 ± 205.8	39.03 ± 133.9	0.666

ESH/ESC guidelines,[21,23] was substantially reduced in both treatment groups. Third, tolerability was high, with 0.8% of patients experiencing adverse events in the fixed-combination and 1.2% in the high-dose monotherapy group. Fourth, physicians chose to use high-dose monotherapy in patients with more advanced disease.

Blood pressure reduction in CHILI Triple T in perspective

Clinical trials evaluating candesartan monotherapy or candesartan/HCTZ combination therapy consistently show safe and effective blood pressure reduction.[7,24–29] Furthermore, there is evidence from a study published by Ohma et al that the ARB candesartan is more effective compared with the first-generation ARB losartan. The reduction in blood pressure and the proportion of patients with normalized blood pressure were greater with the candesartan 16 mg and HCT 12.5 mg combination than with the losartan 50 mg and HCT 12.5 mg combination,[30] supporting the interpretation that not all ARBs are similarly effective. The antihypertensive effect of candesartan and HCT has been shown to be dose related over a wide range of doses, and the effects of the components are fully

Table 5 Number of patients with adverse events or serious adverse events during the survey and adverse events coded by MedDRA® Version 11.1 (safety population: n = 4600)

	Candesartan 16 mg + hydrochlorothiazide 12.5 mg (n = 3337)		Candesartan 32 mg (n = 1263)	
	n	%	n	%
No adverse events	3313	99.3	1245	98.6
Any adverse events	24	0.7	18	1.4
Serious adverse events	1	0.0	2	0.2
Not serious	23	0.7	16	0.9
MedDRA® primary system organ classes				
Adverse events	24	100	18	100
General disorders and administration site conditions	1	4.2	1	5.6
Skin and subcutaneous tissue disorders	3	12.5	1	5.6
Respiratory, thoracic, and mediastinal disorders	4	16.7	6	33.3
Gastrointestinal disorders	3	12.5	1	5.6
Nervous system disorders	2	8.3	1	5.6
Vascular disorders	5	20.8	1	5.6
Cardiac disorders	4	16.7	4	22.2
Musculoskeletal and connective tissue disorders	1	4.2	1	5.6
Investigations	1	4.2	1	5.6

additive.[31] The present study comparing high-dose candesartan 32 mg monotherapy with candesartan and HCTZ combination therapy revealed similar effective blood pressure reduction of both treatment regimens (Figure 1) independent of the baseline risk stratification (Figure 2). A higher baseline risk (which corresponds to a higher blood pressure at baseline) consistently resulted in a more pronounced blood pressure reduction of the respective treatment regimen. These results support the use of both treatment regimens for hypertensive patients, spanning the complete risk spectrum of hypertension-induced complications independent of risk at baseline.

High-dose monotherapy versus dual-combination treatment

Based on the results of the present study, both treatment regimens were similarly effective at reducing blood pressure. Systolic blood pressure reduction was slightly more pronounced in the high-dose monotherapy group, but this difference disappeared when grouping patients according to baseline grade of hypertension (Figure 1).

The rationale for combining an ARB with HCTZ is that the mechanism of action is complementary and RAAS blockade augments the blood pressure-lowering efficacy of diuretics while alleviating their adverse effects. Thiazide diuretics lower blood pressure through natriuresis, resulting in volume depletion and reduction of peripheral vascular resistance over time.[32,33] Combining an ARB with a diuretic reduces vasoconstriction mediated by angiotensin II, at the same time reducing volume and enhancing the efficacy of both antihypertensive components. Therefore, combination therapy may help patients attain blood pressure control in a timelier manner. To achieve this, ARBs at a standard dose are usually combined with low-dose diuretics.[34] The rationale to use high-dose ARBs is their proven protective effect for end-organs. Their particular benefit relates to their protective effect on end-organs such as the heart,[8–11] kidneys,[12–16] and brain.[17,18] However, results were usually obtained with high doses of candesartan cilexetil, such as 32 mg or even higher, as applied in the SMART (Supra Maximal Atacand Renal Trial).[34] An advantage of including a high-dose ARB in antihypertensive treatment is the low rate of adverse events associated with this class compared with other antihypertensive agents.[35,36] Both ARB and HCTZ combination and ARB monotherapy have been shown to be associated with a low rate of treatment discontinuations.[37] Taking into account these considerations, a further rational approach would be to make use of the end-organ protective effect using 32 mg of an ARB and combining this dose with HCTZ as outlined previously. This has been shown to be effective in clinical trials, and

further clinical practice research is ongoing.[29] We were able to show that younger people aged $\leq$ 65 years, patients with dyslipidemia, smokers, patients with a prior cardiovascular event, and patients with microalbuminuria had improved blood pressure reduction in the high-dose candesartan monotherapy group compared with patients without the respective condition. Physicians were also more likely to assign high-dose monotherapy to patients with pre-existing (vascular) disease. These findings are in accordance with observations showing that the use of an ARB reduces both proteinuria and the rate of deterioration of renal function beyond those seen with equivalent blood pressure reduction from conventional antihypertensive agents.[12–16] In particular, proteinuria has been a marker of kidney disease, and recent research has shown that renal and cardiovascular outcomes seem to correlate with the pretreatment levels of proteinuria and with the reduction of proteinuria with treatment.[38–42] In the present trial, patients on candesartan experienced higher reductions in microalbuminuria in the candesartan high-dose arm compared with the candesartan and HCTZ combination treatment arm, although this change did not reach statistical significance. However, patients with prior microalbuminuria responded to candesartan with increased blood pressure reduction, which might reflect organ-protective effects of high-dose RAAS blockade.

Classification of cardiovascular risk and impact of candesartan cilexetil treatment

The ESH/ESC guidelines recommend total cardiovascular risk evaluation in every patient in order to refine pharmacotherapy. The blood pressure threshold at which to commence drug administration, the target blood pressure to be reached by drug treatment, and the decision to use two-drug combinations as an initial treatment step are influenced by this classification.[43] The 2009 update of this guideline now underlines that the presence of subclinical organ damage results in cardiovascular risk to be in the high range, ie, an absolute risk of at least 20 cardiovascular events in 100 patients within 10 years.[44] The update further expresses that there is indisputable evidence that major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events such as stroke and myocardial infarction.[44]

We were able to demonstrate with this noninterventional study that added cardiovascular risk is substantially lowered with either high-dose mono- or combination therapy including candesartan cilexetil. Although several two-drug combinations are suitable for clinical use, outcome trials point to a favorable role of combining RAAS blocking agents

with diuretics.[45] Further, there is a particular role for ARBs, eg, candesartan cilexetil, in patients with diabetes.[44]

Limitations

The present results have to be considered against the background of potential limitations. The study was not controlled, and therefore the role of a placebo effect or the withdrawal of antihypertensive agents is unknown. Second, in the absence of a randomization procedure, the influence of unknown biases, eg, through patient selection, cannot be ruled out. Thus, we observed more patients with higher risk and more concomitant diseases in the monotherapy group. This selection clearly indicates that physicians preferred monotherapy in the group with higher risk and avoided diuretic impairment. Concomitant diuretic prescription could be due to a higher rate of kidney disease. Third, changes in concomitant medication influencing the metabolic profile (eg, lipid-lowering drugs, oral antidiabetic agents, or insulin) have not been documented in the present study. However, it should be kept in mind that observational studies in primary care, including typical patient groups and reflecting current treatment approaches, are useful for complementing the findings of randomized controlled trials.[46]

Conclusion

Both the fixed-dose combination of candesartan cilexetil 16 mg and HCTZ 12.5 mg and high-dose monotherapy with candesartan 32 mg are highly effective and safe for lowering blood pressure in patients at increased cardiovascular risk with mild, moderate, or severe hypertension. The choice of either strategy therefore largely depends on the principal aim: blood pressure reduction with pronounced volume restriction or pronounced additional end-organ protection.

Authors' contributions

Takeda Pharma GmbH designed the study. Peter Bramlage explored the data, requested statistical analyses from the clinical research organization (responsible statistician Dr Frank Romanowski), and wrote the first draft of the manuscript with Gerd Bönner. Bernhard Landers revised the manuscript for important intellectual content. All authors reviewed and approved the final manuscript.

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Disclosure

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