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ORIGINAL ARTICLE

Evaluation of the effects of fixed combinations of sustained-release verapamil/trandolapril versus captopril/hydrochlorothiazide on metabolic and electrolyte parameters in patients with essential hypertension

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The objective of this randomised open, active controlled, cross-over study was to evaluate the effect of a fixed combination of verapamil SR/trandolapril compared to captopril/hydrochlorothiazide on serum lipids, lipoproteins, and other metabolic and electrolyte parameters in patients with essential hypertension. Another objective was to assess the efficacy and safety of both combinations. One hundred hypertensives with systolic blood pressure 140–209 mm Hg and diastolic blood pressure 90–119 mm Hg were evaluated after 16 weeks receiving a fixed combination of verapamil SR 180 mg/trandolapril 2 mg (VT) or captopril 50 mg/hydrochlorothiazide 25 mg (CH) both given once daily. Lipids and lipoproteins were assessed in duplicate on 2 consecutive days. The study was completed by 80 patients. There was no statistically significant difference between the two combined regimens with respect to low-density lipoprotein (LDL)-cholesterol for the 'intention-to-treat' population measured at the end of each treatment period (3.44 ± 0.87 mmol/L with VT, and 3.46 ± 0.86 mmol/L with CH). No differences were found for other lipid parameters like total cholesterol, triglycerides, apolipoproteins A1 and B, Lp(a). High-density lipoprotein (HDL)-cholesterol was significantly higher with VT (1.39 ± 0.01 *vs* 1.35 ± 0.01, $P < 0.03$). Serum potassium declined while uric acid and glucose increased on CH. In conclusion, no significant differences were found in LDL-cholesterol and in other lipid parameters with the exception of HDL-cholesterol which was significantly higher on VT. Serum potassium declined while uric acid and glucose increased on CH (all significantly). Both fixed combinations were well tolerated. The incidence of adverse events was higher on CH. Both fixed combinations significantly lowered BP.

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Introduction

Despite the tremendous progress in cardiovascular pharmacotherapy, hypertensive patients still have higher cardiovascular morbidity and mortality than their normotensive controls.[1] One of the possible explanations is the fact that hypertension is quite frequently associated with other cardiovascular risk factors, eg, lipid disorders, obesity, and diabetes.[2]

A variety of antihypertensive drugs are now available for the treatment of hypertension. Most of these drugs are not ideal in terms of lowering blood pressure (BP) in all patients without causing side effects. The current WHO/ISH guidelines[3] emphasise the use of six major classes of antihypertensive drugs: diuretics, beta-blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, alpha-blockers and angiotensin II antagonists whereas the 6th Joint National Committee on the Treatment, Detection and Follow-up of High Blood Pressure[4] prefers to initiate antihypertensive treatment in uncomplicated cases with beta-blockers or diuretics.

Clinical trials proved that diuretics and beta-blockers lower BP and reduce cardiovascular morbidity and mortality; however, the effect of these drugs on coronary heart disease was less beneficial than expected.[5]

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Thiazides and loop diuretics increase total, low-density lipoprotein (LDL)- and very low-density lipoprotein (VLDL)-cholesterol while high-density lipoprotein (HDL)-cholesterol remains unchanged.[6] Similarly, beta-blockers induce a moderate increase in total triglycerides and a mild decrease in HDL-cholesterol.[6,7] Considering that lipids (increase in total and LDL-cholesterol and decrease in HDL-cholesterol) are a strong risk factor, an increase in cholesterol levels may offset the benefit obtained by lowering BP.[8]

These metabolic changes may increase the risk of cardiovascular disease and contribute to the progression of arteriosclerosis and reduce the benefits of antihypertensive treatment.

Calcium antagonists and ACE inhibitors do not induce undesirable side effects on lipids and lipoproteins.[9]

A recent paper[10] tested long-term (1 year) effects of six different antihypertensive drugs (hydrochlorothiazide, atenolol, captopril, clonidine, diltiazem HCl, prazosin) and placebo on plasma lipids and lipoprotein profiles in a multicentre randomised double-blind parallel-group clinical trial in 15 US Veterans' Affairs medical centres. Surprisingly, none of these six antihypertensive drugs has any long-term adverse effects on lipids and lipoproteins.

According to current national and international guidelines,[3,4] treatment of mild to moderate hypertension is started with a single agent. All intervention trials demonstrated that more than 50% of patients need a combination[11] to achieve a BP below 140/90 mm Hg. Combining two drugs may reduce BP by several mechanisms of action and obtain additive or potentiated effects. By using low doses of drugs, side effects are minimised and patient compliance may improve.

Angiotensin-converting enzyme inhibitors and calcium-channel blockers have favourable haemodynamic and biochemical profiles as well as patient convenience and quality of life. These classes of antihypertensives have shown cardioprotective[12–16] and nephroprotective[17,18] effects as well as lack of adverse metabolic effects. A combination of these classes may potentially offer benefits over other combined regimens. The present study was designed to compare the effect of such a fixed combination containing 180 mg of sustained-release verapamil and 2 mg of trandolapril with a traditional combination of 50 mg of captopril and 25 mg of hydrochlorothiazide on lipid parameters in essential hypertensives.

Patients and methods

Patients

A total of 100 Caucasian patients (81 men and 19 women) aged 18–75 years with mild to moderate essential hypertension (systolic BP (SBP) 140–209 mm Hg and diastolic BP (DBP) 90–119 mm Hg) were enrolled into the study. Patients were eligible for the study if they were newly diagnosed hypertensives or those whose BP was currently inadequately controlled, or their current antihypertensive therapy was not well tolerated. Their total cholesterol had to be $\leqslant$7 mmol/L and LDL-cholesterol $\leqslant$6 mmol/L while not taking lipid-lowering drugs.

Exclusion criteria included secondary hypertension, cerebral haemorrhage within the last 6 months, stroke or transient ischaemic attack, myocardial infarction within the last 3 months, unstable angina, decompensated congestive heart failure, mitral valve stenosis, aortic stenosis, or hypertrophic cardiomyopathy, sinoatrial block with a heart rate $<$50/min, second- or third-degree atrioventricular block, sick sinus syndrome, atrial fibrillation/flutter, pre-excitation syndrome, known collagen or autoimmune disease, angioneurotic oedema, kidney transplant, clinically relevant liver disease, or impaired renal function (serum creatinine $>$1.8 mg/dL and/or creatinine clearance $<$30 mL/min), clinically relevant electrolyte imbalance (eg, serum potassium values $<$3.5 mmol/L, or $>$5.5 mmol/L), clinically relevant gallbladder and/or bile duct disease, pancreatitis, diabetes, thyroid dysfunction, clinically relevant haematologic disease, pregnancy or breast-feeding, women with childbearing potential had to take oral contraception or have an intra-uterine device (IUD), and any other severe or terminal concomitant disease as well as any condition which may interfere with the absorption of the study medication.

The following concomitant medication was not allowed: any other antihypertensive medication, neuroleptics, antidepressants, allopurinol, lithium-containing drugs, immunosuppressive and/or antineoplastic drugs, chronic systemic glucocorticoid therapy (more than 7 consecutive days in 1 month), antiarrhythmic drugs, anaesthetics/narcotics, long-acting nitrates, lipid-lowering drugs, insulin, oral antidiabetic agents, testosterone, and/or anabolic agents, adrenergic drugs, thyroid hormones, cholagogues and/or choleretic agents.

Chronic therapy (more than 7 consecutive days in 1 month) with non-steroid anti-inflammatory drugs (NSAID) could reduce the efficacy of the test medication. Therefore (if not absolutely indicated), chronic therapy with NSAID was avoided during the study.

The study was approved by the Ethics Committee of the Institute for Clinical and Experimental Medicine in Prague and was conducted in accordance with the Declaration of Helsinki (Hong Kong Revision 1989). A written informed consent had been obtained from each patient prior to entry.

Study design

Computer-assisted randomisation was used to allocate the patients either to treatment with a fixed combination of 180 mg sustained-release verapamil and 2 mg trandolapril (VT) or 50 mg captopril and 25 mg hydrochlorothiazide (CH), each combination being administered in one capsule (VT) or one tablet (CH), once a day after breakfast. After 16 weeks, patients were switched over to the alternative fixed combination for a further 16 weeks, therefore the total duration of the study for each patient was 32 weeks (Figure 1). Patients were examined at a 4-

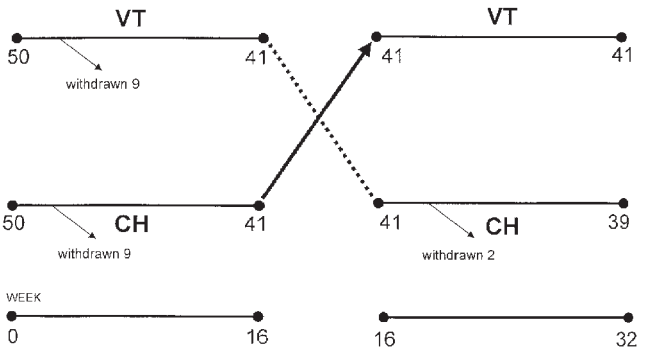

Figure 1 Study design and numbers of patients in various stages of the study. VT, verapamil SR 180 mg/trandolapril 2 mg; CH, captopril 50 mg/hydrochlorothiazide 25 mg.

week interval during the study. They were asked to keep their dietary habits constant during the study period. The same applied to smoking and alcohol consumption.

At entry into the study, the medical history of each subject was assessed and the patient underwent a physical examination. At the initial visit, office BP was read on both arms, at follow-up visits, only on the arm showing a higher mean diastolic reading (calculated mean for three readings) initially.

At each visit, sitting systolic and diastolic BP and heart rate were recorded. Body weight was recorded every 4 weeks. Twelve-lead electrocardiography, blood sampling for routine clinical chemistry and haematology variables, semiquantitative urinalysis and 24-h ambulatory BP monitoring (ABPM) were performed at entry, at week 16 and at the end of the study. Lipids and lipoproteins were assessed in duplicate on 2 consecutive days (ie, four measurements) at entry, weeks 16 and 32.

Office BP was measured between 8.00 am and 10.00 am in accordance with the recommendations of the British Hypertension Society[19] using a conventional mercury sphygmomanometer (Erkameter, Germany). After the patient had rested for 10 min, the sitting BP was measured three times at 2-min intervals before intake of the study medication. The diastolic pressure reading was identified by the disappearance of Korotkoff phase V sounds. The patient's arm used for BP reading was elevated to the level of the heart using a suitable support. Means of the three consecutive sitting measurements were recorded as the sitting BP for that visit.

Twenty-four hour ABPM was performed in accordance with the recommendations of the German Hypertension League[20] on the non-dominant arm using Spacelabs equipment, model 90207 (Spacelabs, Redmont, WA, USA),[21] after validation of its readings against those of a mercury sphygmomanometer. The device was set to obtain automatic BP readings at 15-min intervals during the daytime (6.00 am to 10.00 pm) and 60-min intervals during the night-time (10.00 pm to 6.00 am). The patient was sent home with instructions to attend to his/her usual daily activities, but to hold their arm still at the time of the measurements, note in a diary his/her location (clinic, at home, at work, other), posture (sitting, standing or reclining) and activity (walking, talking, engaged in paper work, etc) at the time of each BP reading. A minimum of 48 readings was required during 24-h ABPM.

Compliance with treatment was assessed by routine capsule/tablet counts of the returned study medication. Patients had to be withdrawn if less than 80% and more than 120% of the study medications were taken. Adverse events were recorded at each visit.

Patients had to be withdrawn prematurely if at least 8 weeks of treatment with either regimen DBP was $\geqslant$100 mm Hg (two consecutive visits).

Laboratory tests

Lipids and lipoproteins were assessed in duplicate on two consecutive days (ie, four measurements) in a WHO Regional Lipid Reference Laboratory, and mean of all four values was used for statistical analysis. Serum cholesterol and triglyceride levels were measured by fully automated (COBAS MIRA S autoanalyzer) enzymatic method (reagents from Boehringer Mannheim, Germany and Hoffmann-LaRoche, Basel, Switzerland, respectively). HDL-cholesterol was determined by the same method after precipitation of serum lipoproteins with sodium phosphotungstate and magnesium chloride (kits from Boehringer Mannheim, Germany). LDL-cholesterol was determined by PVS method (Boehringer Mannheim, Germany). ELISA method (from the same manufacturer) was used for lipoprotein(a) determination. Apoprotein A1 and apoprotein B were assessed by turbidimetric method using the laboratory's own purified antibodies. Fibrinogen was measured using nephelometry (SFL, UK).

Glucose was analysed enzymatically (Lachema Brno, Czech Republic). All other parameters (haemoglobin, haematocrit, red cells, white cells including differential leukocyte count, platelets, ASAT, ALAT, GGT, LDH, alkaline phosphatase, serum amylase, total bilirubin, blood urea nitrogen (BUN), uric acid, creatinine, total protein, serum sodium, serum calcium, serum potassium) were routinely evaluated at the Department of Special Laboratories of the Institute for Clinical and Experimental Medicine, Prague. Urine was assessed semiquantitatively using Combur 9 strip test (Boehringer Mannheim, Germany).

Statistical methods

Based on literature data,[22] it was assumed that untreated hypertensives have a mean LDL-cholesterol value of 4.4 mmol/L. The sample size estimates were based on detecting a 0.44 mmol/L difference in LDL-cholesterol levels (assuming a standard deviation of 0.9 mmol/L) between treatment groups with a statistical power of at least 80% and significance level of 5% (two-sided). This indicated 68 patients completed the study (34 in each treatment sequence). Assuming a drop-out rate of 30%, 100 patients had to be randomised.

An intention-to-treat analysis was used in evaluat-

ing efficacy and safety results. For the efficacy analysis, the last results obtained in patients who did not complete the study were carried forward to subsequent time points. In addition, the primary efficacy parameter, ie, LDL-cholesterol, was also analysed on a 'per protocol' basis, ie, all patients meeting the inclusion and exclusion criteria and completing both treatment periods.

All primary (LDL-cholesterol), secondary (HDL- and total cholesterol, triglycerides, apolipoproteins AI and B and lipoprotein(a)) and further efficacy parameters (24-h BP profile, office DBP, office SBP) were analysed using statistical methods for cross-over design[23] where a possible carry-over effect and the influence of baseline values were examined in an exploratory analysis. Since no carry-over effect was found, the model included the factors: patient, period, and treatment. The null hypothesis of equal treatment effects was tested at the two-sided 5% level. Also two-sided 95% confidence intervals were provided.

Results

A total of 100 patients entered the study, 50 of them were randomly allocated to treatment with sustained-release of verapamil/trandolapril (VT), followed by captopril/hydrochlorothiazide (CH), and 50 patients were randomized to receive the two treatments in the opposite sequence. A total of 20 patients were withdrawn prematurely: 18 during the first treatment period (nine while treated with VT and nine while treated with CH), and two during the second treatment period, both while treated with CH (Figure 1). An overview of the reasons for withdrawal is given in Table 1. The most frequent cause of premature termination was unsatisfactory therapeutic response (because of safety reasons, patients had to be withdrawn prematurely if DBP was $\geqslant$100 mm Hg after at least 8 weeks' treatment on two consecutive visits) followed by adverse events, non-compliance, and protocol violations.

The overall compliance to study medication was very good (99.6% during VT and 100% during CH for all randomised patients).

Both treatment groups were similar with respect to demographic and baseline characteristics (Table 2). Hypertension was newly diagnosed only in four patients.

Efficacy

Primary efficacy parameter: The primary efficacy parameter was LDL-cholesterol which did not show any statistically significant differences between the two treatments for the 'intention-to-treat' population measured at the end of each treatment period, as determined by ANOVA including the effects of patient, period, and treatment ($P = 0.909$, Table 3). Results obtained for the 'per protocol population' were similar with an estimated group difference of –0.18 (95% CI: –0.147 to 0.112, $P = 0.7881$).

Secondary efficacy parameters: All secondary lipid parameters (Table 3) remained unaltered except for HDL-cholesterol which was significantly higher with VT (1.39 ± 0.01 *vs* 1.35 ± 0.01, $P < 0.03$). The same ANOVA model as that for the analysis of the primary efficacy parameter was used.

Other laboratory parameters: The other laboratory parameters are listed in Table 4. Serum potassium declined while uric acid and glucose increased on CH (all significantly). Serum creatinine, urea, and fibrinogen did not differ significantly. With respect to potassium, 20 patients developed serum potassium values $\leqslant$3.8 mmol/L while treated with CH whereas only two while treated with VT ($P < 0.05$). In summary, the incidence of moderate to severe

Table 1 Basic study characteristics

	No. of patients		
	VT/CH	*CH/VT*	*Total*
Randomised	50	50	100
Entered period 1	50	50	100
Completed period 1	41	41	82
Withdrawn during period 1[a]	9	9	18
for unsatisfactory therapeutic response	5	8	13
for adverse events (AEs)	3	3	6
for non-compliance	2	0	2
for withdrawal of informed consent	1	0	1
met exclusion criteria/protocol violation	2	0	2
Entered period 2	41	41	82
Completed period 2	39	41	80
Withdrawn during period 2	2	0	2
for unsatisfactory therapeutic response	2	0	2
Evaluable			
Intention-to-treat analysis of efficacy	41	41	82
Per-protocol analysis of efficacy	38	38	76
Safety	50 VT, 41 CH	50 CH, 41 VT	100

VT, verapamil SR 180 mg/trandolapril 2 mg; CH, captopril 50 mg/hydrochlorothiazide 25 mg; [a]more than one reason for withdrawal per patient possible.

Table 2 Demographic and baseline data; all randomised patients—mean (standard deviation)

	VT/CH (n = 50)	*CH/VT (n = 50)*	*Total* (n = 100)
Sex: Male/Female	46/4	35/15	81/19
Age (yrs)	53 ± 10.3	57 ± 6.7	55 ± 8.8
Body weight (kg)	89 ± 13.9	86 ± 17.3	87 ± 15.7
Duration of hypertension (yrs)	14.7 ± 10.1	13.5 ± 10.2	14.1 ± 10.1
Office SBP (mm Hg)	163 ± 15.6	162 ± 16.7	162 ± 16.1
Office DBP (mm Hg)	103 ± 6.4	103 ± 6.5	103 ± 6.4
Heart rate (bpm)	67 ± 8.3	69 ± 7.9	68 ± 8.1
LDL-cholesterol (mmol/L)	3.533 ± 1.007	3.506 ± 0.657	3.520 ± 0.846
HDL-cholesterol (mmol/L)	1.242 ± 0.331	1.409 ± 0.423	1.325 ± 0.387
Total cholesterol (mmol/L)	5.386 ± 0.995	5.508 ± 0.878	5.447 ± 0.936
Triglycerides (mmol/L)	1.951 ± 1.065	1.766 ± 1.009	1.858 ± 1.036
Apolipoprotein A1 (g/L)	1.301 ± 0.191	1.388 ± 0.249	1.344 ± 0.225
Apolipoprotein B (g/L)	1.131 ± 0.253	1.111 ± 0.202	1.121 ± 0.228
Lipoprotein (a) (mg/L*)	5.6 (5–216)	7.1 (5–89)	6.2 (5–216)

VT, verapamil SR 180 mg/trandolapril 2 mg; CH, captopril 50 mg/hydrochlorothiazide 25 mg. *Median (range).

Table 3 Summary of primary and secondary lipid parameters by treatment 'intention-to-treat' population

	Baseline	*VT*	*CH*	*VT-CH*	*P*
LDL-chol (mmol/L)	3.49 ± 0.87	3.45 ± 0.87	3.46 ± 0.89	–0.07 ± 0.562	NS
HDL-chol (mmol/L)	1.35 ± 0.18	1.39 ± 0.38	1.35 ± 0.38	0.040 ± 0.161	0.03
Total chol (mmol/L)	5.43 ± 0.97	5.42 ± 0.92	5.41 ± 0.95	0.007 ± 0.575	NS
Triglycerides (mmol/L)	1.81 ± 1.04	1.70 ± 0.94	1.72 ± 0.85	0.015 ± 0.642	NS
Apo-A1 (g/L)	1.35 ± 0.23	1.40 ± 0.22	1.38 ± 0.22	0.021 ± 0.14	NS
Apo-B (g/L)	1.12 ± 0.24	1.11 ± 0.25	1.12 ± 0.24	–0.007 ± 0.162	NS
Lp(a) (mg/L*) (range)	6.2 (5.0–152.5)	8.1 (5.0–104.7)	5.0 (5.0–98.7)	0.0 (–36.6–+77.3)	NS

VT, verapamil SR 180 mg/trandolapril 2 mg; CH, captopril 50 mg/hydrochlorothiazide 25 mg. *Presented as median (range), all other values presented as mean ± s.d.

Table 4 Summary of other laboratory parameters 'intention-to-treat' population

	Baseline	*VT*	*CH*	*VT-CH*	*P*
Sodium (mmol/L)	145.1 ± 2.7	145.5 ± 2.3	145.6 ± 2.3	–0.1 ± 2.4	NS
Potassium (mmol/L)	4.24 ± 0.32	4.41 ± 0.36	4.11 ± 0.36	0.30 ± 0.40	0.001
Glucose (mmol/L)	5.17 ± 0.49	5.13 ± 0.67	5.33 ± 0.69	–0.20 ± 0.68	0.001
Urea (mmol/L)	5.22 ± 1.23	5.62 ± 1.17	6.13 ± 1.49	–0.51 ± 1.24	NS
Creatinine (μmol/L)	95 ± 11.2	95.7 ± 12.5	99.7 ± 13.3	–0.4 ± 9.8	NS
Uric acid (μmol/L)	366 ± 83	350 ± 79	418 ± 83	–68.6 ± 50.8	0.001
Fibrinogen (g/L)	3.51 ± 0.77	3.43 ± 0.77	3.40 ± 0.67	0.05 ± 0.91	NS

VT, verapamil SR 180 mg/trandolapril 2 mg; CH, captopril 50 mg/hydrochlorothiazide 25 mg.

changes in abnormal laboratory values was higher on CH as compared with VT.

Twenty-four hour ABPM: Table 5 summarises the ANOVA results for mean 24-h, daytime (ie, 6.00 am to 11.00 pm), and night-time (ie, 11.00 pm to 6.00 am) SBP, DBP, and heart rate for the 'intention-to-treat' population. With respect to adjusted mean DBP, almost no differences between VT and CH were seen. Adjusted mean SBP was slightly higher on treatment with VT than that with CH in all three means. These differences reached statistical significance for the 24-h and night-time means, although the absolute adjusted mean treatment difference was only 2.3 mm Hg for the 24-h mean and 3.5 mm Hg for the night-time mean, which can be explained by small variance and relatively large sample size.

Office BP measurement: The results of the ANOVA at the last visit during each treatment period are summarised in Table 6 for the 'intention-to-treat' population. At the last visit of each treatment, adjusted mean sitting SBP and DBP was higher on VT.

The number of patients who achieved DBP $<$90 mm Hg at the end of each treatment did not differ (56% VT *vs* 46% CH, NS).

Safety

The overall incidence of adverse events was higher on CH than on VT, the frequency of serious adverse events and adverse events leading to withdrawal from the study was similar for both treatment regimens (Table 7).

Table 5 ANOVA results for mean 24-hourly, daytime and night-time SBP, DBP and heart rate determined by ABPM, intention-to-treat population; adjusted mean (95% confidence interval)

	24-hour[a]	*Daytime*[a]	*Night-time*[a]
Systolic blood pressure (mm Hg)			
VT	128.3 (126.9; 129.7)	131.7 (130.3; 133.2)	121.3 (119.4; 123.3)
CH	125.9 (124.5; 127.3)	130.1 (128.6; 131.5)	117.8 (115.9; 119.8)
Difference[b]	2.3 (0.3; 4.3)	1.7 (–0.4; 3.7)	3.5 (0.8; 6.3)
P-value	0.0223	0.1115	0.0125
Diastolic blood pressure (mm Hg)			
VT	80.3 (79.4; 81.2)	83.7 (82.6; 84.8)	73.3 (72.0; 74.6)
CH	80.1 (79.1; 81.0)	84.3 (83.2; 85.4)	71.9 (70.6; 73.3)
Difference[b]	0.2 (–1.1; 1.5)	–0.5 (–2.1; 1.0)	1.4 (–0.5; 3.3)
P-value	0.7367	0.5078	0.1507
Heart rate (bpm)			
VT	71.0 (70.1; 71.9)	75.1 (74.1; 76.1)	63.0 (61.9; 64.1)
CH	75.0 (74.1; 75.9)	79.6 (78.6; 80.6)	65.7 (64.6; 66.9)
Difference[b]	–4.0 (–5.3; –2.7)	–4.5 (–5.9; –3.1)	–2.8 (–4.4; –1.2)
P-value	<0.001	<0.001	0.001

[a]Estimates from the ANOVA model outcome = patient + period + treatment; [b]VT minus CH.
VT, verapamil SR 180 mg/trandolapril 2 mg; CH, captopril 50 mg/hydrochlorothiazide 25 mg.

Table 6 ANOVA results for office BP measurements (mm Hg) at the last visit under each treatment, intention-to-treat population (n = 82); adjusted mean, 95% confidence interval

	ANOVA (n = 82)	
	Adjusted mean	*95% CI*
SBP		
Baseline	161.1	(157.7; 164.5)
VT[a]	144.0	(142.2; 145.9)
CH[a]	139.5	(137.7; 141.3)
Difference[a,b]	4.5	(2.0; 7.1)
P-value for diff.[a]	<0.001	
DBP		
Baseline	101.9	(100.7; 103.1)
VT[a]	90.6	(89.7; 91.4)
CH[a]	88.7	(87.8; 89.6)
Difference[a,b]	1.9	(0.6; 3.1)
P-value for diff.[a]	0.0037	

VT, verapamil SR 180 mg/trandolapril 2 mg; CH, captopril 50 mg/hydrochlorothiazide 25 mg.
[a]From the ANOVA model outcome = patient + period + treatment, or the respective mixed ANOVA model with patients specified as random effects.
[b]VT minus CH.

Table 7 Summary of adverse events (AEs)

No. (%) of patients with	*VT (n = 91)*	*CH (n = 91)*
AEs	53 (58)	67 (74)
At least likely drug-related AEs	4 (4)	11 (12)
AEs of severe intensity	9 (10)	5 (5)
AEs resulting in withdrawal	3 (3)	3 (3)
Serious AEs	2 (2)	2 (2)

VT, verapamil SR 180 mg trandolapril 2 mg; CH, captopril 50 mg/hydrochlorothiazide 25 mg.

Six patients were withdrawn from the study due to adverse events, three of them while being treated with VT and the other three while being treated with CH, all during the first study period. In none of the cases was there a causal relationship between the adverse event and the study drug.

Discussion

This study failed to demonstrate any difference in LDL-cholesterol due to a fixed combination of verapamil SR/trandolapril or that of captopril/hydrochlorothiazide. The original statistical estimation assumed that untreated hypertensives have a mean LDL-cholesterol value of 4.4 mmol/L. The baseline mean cholesterol value for our group of patients was much lower (3.52 ± 0.846 mmol/L; n = 100). This was partly caused by the inclusion criteria which did not allow the inclusion of anyone with total cholesterol >7 mmol/L and LDL >6 mmol/L, because these hypertensive patients should be, according to current guidelines,[24] treated with lipid-lowering drugs. Over a period of 12 years, there has also been a statistically significant decline in the mean total cholesterol value in a middle-aged random population sample in the Czech Republic.[25] From this point of view, both fixed combinations were identical and did not produce any harm to the main atherogenic risk factor which is LDL cholesterol.

HDL-cholesterol was significantly higher on VT. However, the difference of 0.04 ± 0.161 mmol/L has only very little clinical meaning. We have again to underline that the whole group of patients had a relatively favourable mean HDL-cholesterol value (1.325 ± 0.387 mmol/L), which did not differ from a population screening in the Czech Republic.[25] It should be noted that the population data from the Czech Republic were available in 1998 reflecting the situation in 1997/98 and this clinical trial was

designed (including the statistical estimation) in 1993.

The combination verapamil SR and trandolapril has been shown to be metabolically neutral[26] compared to atenolol/chlorthalidone in hypertensive type 2 diabetic patients. The latter combination induced a marked increase in triglycerides.

The lipid neutral effect of the ACE inhibitor/diuretic found in our study is in controversy with Shieh *et al*[27] who followed, in an open-label study, hypertensives whose medication was started with the ACE inhibitor cilazapril, combined with hydrochlorothiazide, if needed, to achieve goal BP. After 26 and 52 weeks of treatment, the group treated only with cilazapril did not differ in BP values from that having hydrochlorothiazide added. However, plasma triglyceride levels tended to be lower in those treated with cilazapril alone. The differences in metabolic parameters between the two treatment groups were considered to be caused by the beneficial effect of ACE inhibitor on the lipid profile in contrast to untoward changes associated with thiazide administration.

Clinically the most important results of this study do belong to the category of safety laboratory parameters. The fixed combination of CH induced a statistically significant decrease in serum potassium and an increase in fasting plasma glucose and uric acid level. This is most likely due to a relatively high dose of hydrochlorothiazide used in this particular combination (25 mg). According to current guidelines,[3,4] lower doses of hydrochlorothiazide (which is 12.5 or even 6.25 mg) are preferred, especially when used in a combination. At the time when the study was designed, the lowest commercially available dose of the fixed combination captopril/ hydrochlorothiazide was captopril 50 mg and hydrochlorothiazide 25 mg.

The cross-over design used in this study enabled to reduce the number of patients completing the study. This was important for planning the study to get reliable lipid results from a WHO Regional Reference Lipid Laboratory. To avoid any potential laboratory inaccuracies due to transport of blood samples, it was decided to perform the study just in one centre at the same site as the lipid laboratory handling only fresh samples.

The baseline laboratory and BP values are definitely affected by the previous antihypertensive treatment as there was no placebo run-in period and the previous antihypertensive treatment had to be stopped at least the day before entering the study. As the main parameters evaluated in this study were lipids, it would be necessary to have a much longer placebo period (probably 8 weeks) than usually performed in trials evaluating antihypertensive drugs. This might not be ethically acceptable. The analysis of variance (ANOVA) performed takes into account the interaction of period (1 or 2) and treatment (VT or CH) for each particular patient.

This cross-over study showed an almost identical BP lowering effect of both fixed combinations. The addition of 25 mg of hydrochlorothiazide has definitely an additive BP-lowering effect on the top of captopril, a short-acting ACE inhibitor. The efficacy and tolerability of this particular combination administered once daily has been documented previously.[28–30] Our study shows 24-h BP control by both combinations maintaining the circadian BP variation.

Fifteen patients were withdrawn from the study due to an unsatisfactory therapeutic response (if after at least 8 weeks of treatment with VT or CH, the DBP values on two consecutive visits were higher than 100 mm Hg). Ten out of these 15 patients were on CH and only five on VT. This is undoubtedly reflected in the BP difference between the two combinations.

The difference in BP reduction between the two treatments is less pronounced when using 24-h ABPM instead of office BP measurement. Almost no differences were seen for 24-h, daytime and night-time means for adjusted mean DBP. Adjusted mean SBP was slightly higher under VT than under CH in all three means with statistical significance for the 24-h and the night-time means.

Although the absolute BP reduction was different, there was no significant difference with respect to target BP in 24-h ABPM. The percentage of systolic hourly means below 140 mm Hg was on average 76% during treatment with VT and 80% during CH. The respective figures for diastolic hourly means below 90 mm Hg were 77% for both treatments.

Generally, the difference in BP reduction is smaller when the more reliable 24-h ABPM instead of office BP measurement is taken.

In conclusion, the fixed combination of verapamil and trandolapril is lipid neutral. In contrast to the combination of ACE inhibitor and diuretic, it does not induce any negative metabolic side effects like hypokalaemia, hyperglycaemia, or increase in uric acid levels. In terms of BP reduction, this combination is comparable with captopril/ hydrochlorothiazide and both combinations are well tolerated. Because of the additional beneficial metabolic effects, the combination of verapamil and trandolapril is a suitable alternative to the traditional one containing an ACE inhibitor and thiazide diuretics for hypertensive patients requiring combination therapy.

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